Lotte Phinè Marie Weijdijk

ORAL HEALTH AND DIABETES: FROM EVIDENCE TO INSIGHTS

Biting into sugar coated data

ORAL HEALTH AND DIABETES: FROM EVIDENCE TO INSIGHTS

Biting into sugar coated data

The studies in this thesis were conducted at the department of Periodontology of the Academic Centre for Dentistry Amsterdam (ACTA). The combined faculty of dentistry of the University of Amsterdam (UvA) and Vrije Universiteit Amsterdam, The Netherlands and the Department of Oral and Maxillofacial Surgery, Amsterdam University Medical Centers, The Netherlands.





The studies in this thesis received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The studies were self-funded by the authors and their respective institutions and the work for papers was funded by regular academic appointments. For chapter 7 a part of the research was supported in kind and made possible by the Clinical for Periodontology "Paro Praktijk Utrecht".



ISBN 9789083340616 Published by DIDES



Design by Sanne Huuskes



Printed by Gildeprint Enschede

Copyright © 2025 L.P.M. Weijdijk, Utrecht, the Netherlands

All rights reserved. No part of this publication may be reproduced or transmitted in any form, by any means, electronic or mechanical, including photocopy, recording or any information storage and retrieval system, without permission of the author.

This thesis was self-funded by the authors and their respective institutions, with no financial support from external parties. The work for this thesis was funded by regular academic appointments at the Academic Center for Dentistry Amsterdam (ACTA) / Amsterdam University Medical Center (UMC) by Slot, van der Weijden, de Lange and Weijdijk.

Publication of this thesis was generously supported by

















Importeur en distributeur van:

Tandpasta mét, en zonder fluoride



ORAL HEALTH AND DIABETES: FROM EVIDENCE TO INSIHGHTS

Biting into sugar coated data

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam op gezag van de Rector Magnificus prof. dr. ir. P.P.C.C. Verbeek

ten overstaan van een door het College voor Promoties ingestelde commissie, in het openbaar te verdedigen in de Aula der Universiteit op woensdag 28 mei 2025, te 14.00 uur

door

Lotte Phinè Marie Weijdijk

geboren te Enschede

PROMOTIECOMMISSIE

Promotores

prof. dr. D.E. Slot Vrije universiteit van Amsterdam

prof. dr. J. de Lange Universiteit van Amsterdam

Copromotores

prof. dr. G.A. van der Weijden Universiteit van Amsterdam

Overige leden

prof. dr. F.R. Rozema Universiteit van Amsterdam

prof. dr. C. Lucas Universiteit van Amsterdam

prof. dr. B.G. Loos Universiteit van Amsterdam

prof. dr. M.F. Timmerman Radboudumc

dr. E. van der Sluijs Universiteit van Amsterdam

dr. R.Z. Thomas Radboudume

dr. M.M. Danser Universiteit van Amsterdam

Faculteit der Tandheelkunde

Paranimfen

Bregje van Swaaij

Emmy Windhorst

TABLE OF CONTENTS

Chapter	1	General introduction	11
Chapter	2	The association of periodontitis with cardiovascular disease parameters – A synthesis of systematic reviews	19
Chapter	3	The association of periodontitis with parameters of diabetes mellitus - A synthesis of systematic reviews	61
Chapter	4	What is the clinical periodontal condition of patients with diabetes mellitus as compared to those without? - A synthesis of systematic reviews	93
Chapter	5	The effect of diabetes on outcomes of non-surgical periodontal therapy - A systematic review with a meta-analysis and trial sequential analysis	121
Chapter	6	DMF scores in patients with diabetes mellitus – A systematic review and meta-analysis	169
Chapter	7	Comparing endodontic treatment prevalence in diabetes mellitus and non-diabetic periodontitis patients - A retrospective case-control investigation	201
Chapter	8	The risk of tooth loss in patients with diabetes - A systematic review and meta-analysis	223
Chapter	9	Edentulism among diabetic patients compared to non-diabetic controls - A systematic review and meta-analysis	261
Chapter	10	Discussion, summary and conclusion	283
Chapter	11	Appendices Nederlandse samenvatting Contributing authors List of abbreviations Aubout the author PhD portfolio Dankwoord	305

"Ik heb het nog nooit gedaan, dus ik denk dat ik het wel kan"

Pippi Langkous

CHAPTER ONE

General introduction



Global health context

As of 2025, approximately 8 billion people live on our planet. Among these, over 1.4 billion individuals (17.5%) are affected by a variety of health conditions, ranging from acute illnesses to chronic diseases. The impact of these health challenges is profound, affecting not only physical health but also diminishing quality of life. This underscores the importance of addressing these widespread health issues in order to reduce the global burden of disease and enhance overall human well-being.

Non communicable diseases

The quality of life can easily be reduced by noncommunicable diseases (NCDs).⁴ They tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioral. NCDs are related with a high mortality rate and are responsible for 71% of all deaths globally. Of these cardiovascular diseases (CVDs) account for most deaths with 17.9 million people annually, followed by cancers (9.3 million), chronic respiratory diseases (4.1 million), and diabetes mellitus (DM) (2.0 million).⁵ DM and CVD are often co-morbidities, with individuals affected by DM facing a two to four times higher risk of developing CVD compared to those without DM.^{6,7} Type II DM is a common metabolic disorder predisposing to diabetic cardiomyopathy and atherosclerotic CVD, which can lead to heart failure through a variety of mechanisms.⁸

Cardiovascular disease

CVDs as defined by the World Health Organization (WHO)⁹ are a group of disorders affecting the heart and blood vessels and could be divided into cardiovascular disease (CVD), including cerebrovascular disease, coronary heart disease, atherosclerotic cardiovascular disease, and peripheral vascular disease, and cardiovascular events (CVE).¹⁰ CVD, which is often asymptomatic, has the potential to result in acute CVE such as myocardial infarction and stroke, making it a prominent global cause of death.^{11,12}

Diabetes

DM is a chronic, metabolic disease characterized by elevated levels of blood glucose levels, resulting in abnormalities in insulin secretion, action or both.¹³ Based on its etiology and pathology, DM is classified into several types, with type I and type II being the most common. Type I classically result from defects in the insulin release from autoimmune destruction. leading to absolute insulin deficiency, while type II caused by an acquired resistance and relative insulin deficiency to insulin in the body.^{13,14} Other forms of DM include gestational DM (GDM), which can occur during pregnancy and other specific types derived from other causes such as genetic insulin abnormalities, pancreatic pathologies, and medications. 15 As stated above, the condition affects millions worldwide and presents a significant public health challenge; with a prevalence of 10.5% of the global population aged 20-79 years who is currently affected, with almost half of these individuals being unaware that they are living with this condition due to the absence of symptoms or disease related knowledge. It is expected that 592 million individuals in 2035 have been diagnosed with DM17 and will increase to approximately 783 million in 2045.16 The prevalence of DM in the Netherlands is estimated to be around 5-6% of the population, including both diagnosed and undiagnosed cases. Data reported by Dutch general practices in 2019 shown 1.1 million people diagnosed with DM. Based on demographics trends it is expected that this number will increase to 1.3 million by 2024.18

Diabetes and oral health

DM is associated with a wide range of complications, including periodontal diseases affecting the oral cavity. Oral health is a fundamental component of general, physical and mental well-being and it's defined by the World Dental Federation as follows:

"Oral health is multi-faceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow and convey a range of emotions through facial expressions with confidence and without pain, discomfort and disease of the craniofacial complex". 19

It is estimated that oral diseases affect 3.5 billion people worldwide. ²⁰ Oral diseases are among the most prevalent diseases globally and have serious health and economic burdens, greatly reducing quality of life for those affected. The most common oral diseases, such as periodontitis and caries, are associated with the four leading NCDs that cause the most deaths²¹ with DM receiving the most significant focus in the literature. More than 90% of DM patients report to have oral manifestations²², such as hyposalivation, burning mouth sensation, taste alteration, halitosis and candidiasis.²³ Conversely, periodontitis has been specifically linked to difficulties in achieving glycemic control and may contribute to the development of worsening DM-related complications, such as CVD.

Periodontitis

Periodontitis is a chronic multifactorial inflammatory disease and causes destruction of the tooth-supporting apparatus. ²⁴ It shows irreversible destruction of the tissues supporting the teeth including the root cementum, periodontal ligament and alveolar bone. Periodontitis is a major public health problem because of its high prevalence, being the most common chronic inflammatory NCD of humans, ²⁵ and affects 20–50% of the global population. ²⁶ Several studies have shown an association between DM and periodontal disease. Both conditions are chronic, inflammatory, and multifactorial, with inflammation being a hallmark of their pathogenesis. ²⁷ A large number of case-reports, cross-sectional studies, longitudinal studies and reviews report on the potential adverse effects of DM on the onset, progression and severity of periodontitis. Recent scientific evidence has also pointed to a bidirectional relationship between periodontal disease and DM. ^{28–30}

Dental caries

Dental caries is one of mankind's most common diseases. The WHO Global Oral Health Status Report estimated that 2 billion people suffer from caries of permanent teeth and 514 million children suffer from caries of primary teeth.³¹ Caries is characterized by the demineralization of tooth enamel caused by involving a complex interaction over time between acid-producing bacteria, fermentable carbohydrates, and many host factors including teeth and saliva, and lifestyle related factors such as high numbers of cariogenic bacteria, inadequate salivary flow, insufficient fluoride exposure, poor oral hygiene and poverty.³² It is suggested that in DM, the caries process is likely enhanced due to a decreased salivary flow rate and expanded levels of glucose in the saliva also emerging from the crevicular fluid.^{33,34} If caries is left untreated or treatment is unsuccessful, it can advance into deeper lesions, eliciting responses from the dental pulp that may ultimately result in necrosis and eventually tooth loss.³⁵

Tooth loss

Both periodontitis and caries are the major cause of tooth loss. If left untreated, both ultimately resulting in edentulism, the condition of being completely without teeth. Extensive tooth loss or edentulism is a major oral health concerns that can lead to difficulties with speaking, low self-esteem and a lowered quality of life.³⁶ It can also impair chewing efficiency which could lead to poor dietary habits by the substitution with easier-to chew food such as those rich in fats and cholesterol.³⁷ Tooth loss has been shown to be associated with obesity,³⁸ which is known as a common risk factor for DM type II, CVD and metabolic syndrome, a cluster of conditions – including also, hypertension, elevated cholesterol levels, and insulin resistance – all of which together increase the risk of these chronic diseases.³⁹

Aims and outlines of this thesis

This thesis explores the relationship of DM with oral health. The following research questions are addressed in this thesis:

- What is the association of periodontitis with CVD/CVE?
- What is the association of periodontitis with parameters of DM?
- What is the severity of periodontal disease in adult patients with DM compared to those without DM?
- What is the effect of DM on periodontal treatment outcomes in patients with periodontitis?
- What is the effect of DM compared to non-DM on the DMF score in adult patients?
- What is the prevalence of endodontic treatment in DM and non-DM patients?
- What is the risk of tooth loss among patients with DM as compared to individuals without DM?
- What is the prevalence of edentulism among DM patients compared to non-DM people established from observational studies?

The majority of the sections in this dissertation have been previously disseminated in international dental science journals. Due to the thematic similarities among certain studies, unavoidable redundancies exist across the chapters. Additionally, minor terminological distinctions arise due to varying specifications imposed by distinct journals. The non-chronological arrangement of the chapters in this dissertation is a deliberate editorial decision.

REFERENCES

- 1. Worldometer. world-population. Accessed May 24, 2024. https://www.worldometers.info/worldpopulation/
- 2. World Health Organization. World Health Statistics. Accessed May 29, 2024. https://www.who.int/data/gho/publications/world-health-statistics
- 3. Centers for Disease Control and Prevention (CDC). Health-Related Quality of Life (HRQOL). 2020. Accessed September 30, 2024. https://archive.cdc.gov.www.cdc.gov/hrqol/index.htm
- 4. Piovani D, Nikolopoulos GK, Bonovas S. Non-Communicable Diseases: The Invisible Epidemic. *J Clin Med.* 2022;11(19). doi:10.3390/jcm11195939
- 5. World Health Organization. Noncommunicable diseases. September 16, 2023. Accessed May 29, 2024. https://www.who.int/news-room/fact-sheets/detail noncommunicable-diseases
- 6. Matheus ASDM, Tannus LRM, Cobas RA, Palma CCS, Negrato CA, Gomes MDB. Impact of diabetes on cardiovascular disease: An update. *Int J Hypertens*. 2013;2013:653789. doi:10.1155/2013/653789
- 7. Emerging Risk Factors Collaboration; Sarwar N, Gao P, Kondapally Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *The Lancet*. 2010;375(9733):2215-2222. doi:10.1016/S0140-6736(10)60484-9
- 8. De Rosa S, Arcidiacono B, Chiefari E, Brunetti A, Indolfi C, Foti DP. Type 2 diabetes mellitus and cardiovascular disease: Genetic and epigenetic links. *Front Endocrinol (Lausanne)*. 2018;9:2. doi:10.3389/fendo.2018.00002
- 9. Cardiovascular diseases (CVDs). Accessed December 23, 2023. https://www.who.int/newsroom/fact-sheets/detail/cardiovascular-diseases-(cvds)
- 10. World Health Organization. Cardiovascular diseases (CVDs). June 11, 2021. Accessed May 29, 2024. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
- 11. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053):1459-1544. doi:10.1016/S0140-6736(16)31012-1
- 12. World Health Organization. The top 10 causes of death. August 7, 2024. Accessed November 20, 2024. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
- 13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013;36(SUPPL.1). doi:10.2337/dc13-S067
- 14. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. *Avicenna J Med.* 2020;10(04):174-188. doi:10.4103/ajm.ajm_53_20
- 15. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(Suppl. 1):S81-S90.
- 16. International Diabetes Federation. *IDF Diabetes Atlas*. 10th ed.; 2021. Accessed May 29, 2024. https://www.diabetesatlas.org
- 17. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103(2):137-149. doi:10.1016/J.DIABRES.2013.11.002
- 18. Nielen M, Poos, R, Korevaar J. Diabetes mellitus in Nederland. Prevalentie en incidentie: heden, verleden en toekomst. Published online 2020:16.
- 19. Glick M, Williams DM, Kleinman DV, Vujicic M, Watt RG, Weyant RJ. A new definition for oral health developed by the FDI World Dental Federation opens the door to a universal definition of oral health. *Br Dent J.* 2016;221(12):792–793. doi:10.1038/sj.bdj.2016.953
- 20. World Health Organization. Oral health data portal. Accessed May 24, 2024.https://www.who.int/data/gho/data/themes/oral-health-data-portal
- 21. Peres MA, Macpherson LMD, Weyant RJ, et al. Oral diseases: a global public health challenge. 2019;394:249-260
- 22. Nazir MA, Alghamdi L, Alkadi M, Albeajan N, Alrashoudi L, Alhussan M. The burden of diabetes, its oral complications and their prevention and management. *Open Access Maced J Med Sci.* 2018;6(8):1545-1553. doi:10.3889/oamjms.2018.294
- 23. Indurkar MS, Maurya AS, Indurkar S. Oral manifestations of diabetes. *Clinical Diabetes*. 2016;34(1):54-57. doi:10.2337/diaclin.34.1.54
- 24. Könönen E, Gursoy M, Gursoy UK. Periodontitis: a multifaceted disease of tooth-supporting tissues. *J Clin Med.* 2019;8(8):1135.
- 25. Herrera D, Sanz M, Shapira L, et al. Association between periodontal diseases and cardiovascular diseases, diabetes and respiratory diseases: Consensus report of the Joint Workshop by the European Federation of Periodontology (EFP) and the European arm of the World Organization of Family Doctors (WONCA Europe). *J Clin Periodontol*. 2023;50(6):819-84l. doi:10.1111/jcpe.13807
- 26. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. *Int J Health Sci* (*Qassim*). Published online 2017:72-80
- 27. Zheng M, Wang C, Ali A, Shih YA, Xie Q, Guo C. Prevalence of periodontitis in people clinically diagnosed with diabetes mellitus: a meta-analysis of epidemiologic studies. *Acta Diabetol.* 2021;58(10):1307-1327.

- 28. Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. *Ann Periodontol*. 2001;6(1):99-112.
- 29. Zainal Abidin Z, Zainuren ZA, Noor E, Mohd Nor NS, Mohd Saffian S, Abdul Halim R. Periodontal health status of children and adolescents with diabetes mellitus: a systematic review and meta-analysis. *Aust Dent J.* 2021;66(1):1-2.
- 30. Stankoa P, Holla Izakovicova L. Bidirectional association between diabetes mellitus and inflammatory periodontal disease. A review. *Biomedical Papers*. 2014;158(1):35-38. doi:10.5507/bp.2014.005
- 31. World Health Organization. Global Oral Health Status Report: Towards Universal Health Coverage for Oral Health by 2030.; 2022. http://apps.who.int/bookorders.
- 32. Selwitz RH, Ismail AI, Pitts NB. Dental caries. *Lancet* . 2007;369(9555):51-59.
- 33. Jawed M, Shahid SM, Qader SA, Azhar A. Dental caries in diabetes mellitus: Role of salivary flow rate and minerals. *J Diabetes Complications*. Published online 2011. doi:10.1016/j.jdiacomp.2010.07.001
- 34. Mascarenhas P, Fatela B, Barahona I. Effect of diabetes mellitus type 2 on salivary glucose A systematic review and meta-analysis of observational studies. *PLoS One*. Published online 2014. doi:10.1371/journal.pone.0101706
- 35. Bergenholtz G, Cox CF, Loesche WJ, Syed SA. Bacterial leakage around dental restorations: its effect on the dental pulp. *J Oral Pathol*. 1982;11(6):439-450.
- 36. Griffin SO, Jones JA, Brunson D, Griffin PM, Bailey WD. Burden of oral disease among older adults and implications for public health priorities. *Am J Public Health*. 2012;102:411-418.
- 37. Ervin RB, Dye BA. The effect of functional dentition on healthy eating index scores and nutrient intakes in a nationally representative sample of older adults. *J Public Health Dent*. 2009;69(4):207-216. doi:10.1111/j.1752-7325.2009.00124.
- 38. Sheiham A, Steele JG, Marcenes W, Finch S, Walls AWG. The relationship between oral health status and Body Mass Index among older people: a national survey of older people in Great Britain. *Br Dent J.* 2002;192(12).
- 39. Ginsberg HN, Maccallum PR. The obesity, metabolic syndrome, and type 2 diabetes mellitus pandemic: Part I. Increased cardiovascular disease risk and the importance of atherogenic dyslipidemia in persons with the metabolic syndrome and type 2 diabetes mellitus. *J Cardiometab Syndr*. 2009;4(2):113-119. doi:10.1111/j.1559-4572.2008.00044.

"Je snapt het pas als je het begrijpt"

Johan Cruijff

CHAPTER TWO

The association of periodontitis with cardiovascular disease parameters

A synthesis of systematic reviews

M.G.P. Schoenmakers, **L.P.M. Weijdijk**, E.J.S. Willems, G.A. Van der Weijden, D.E. Slot *International Journal of Dental Hygiene (submitted)*



ABSTRACT

Focused question

What is the association of periodontal disease and cardiovascular diseases (CVD/CVE) as reported in existing systematic reviews (SRs)?

Methods

MEDLINE-PubMed and Cochrane-CENTRAL databases were searched. Papers that primarily evaluate cardiovascular parameters of cardiovascular disease (CVD) and cardiovascular events (CVE) in periodontitis patients compared to non-periodontitis individuals were included. Data and conclusions as presented in the selected papers were extracted and the potential risk of bias was estimated. A descriptive analysis of the meta-analysis of the selected studies was conducted. A citation analysis was performed, the Bradford Hill criteria were assessed, and the acquired evidence was graded.

Results

Independent screening of 446 reviews resulted in 19 eligible SRs. These were categorized into 13 reviews evaluating CVD and eight evaluating CVE. In total 27 meta-analysis were obtained, the majority (73%) of reported risk ratios and odds ratios are estimated to show a negligible magnitude of the association of periodontitis and CVD. For CVE 46% of the values of the association are considered to be of small magnitude as emerging from 23 meta-analysis. For factors such as gender, age, periodontitis severity, smoking status, and geographic region the statistical significance and magnitude of the association varied. Given the results, a definitive confirmation of causality according to the Bradford Hill criteria was not attainable. With moderate certainty, a predominantly negligible to small magnitude of the association of periodontitis and CVD/CVE was identified.

Conclusion

Based on data collected from existing SRs, the association between periodontitis and CVD/CVE was generally observed to be of negligible to small magnitude. Additionally, the data do not confirm potential causality.

INTRODUCTION

Periodontal disease is a chronic inflammatory disease affecting the tissues that support the teeth, which include the gums, bone, and periodontal ligament.¹⁻³ Estimates suggest that between 20% to 50% of all individuals worldwide are affected by periodontitis, with severe forms of the disease affecting approximately 11% of the global population.⁴⁻⁶ Periodontitis is a major contributor to tooth loss, accounting for 30-35% of all cases. In addition to affecting dental health, periodontitis can lead to difficulties with chewing, negative aesthetic changes and systemic inflammation, significantly impacting the quality of life for those affected.^{12,7} Recent research has suggested that periodontitis may have systemic effects, particularly on cardiovascular health, due to its association with various risk factors such as chronic inflammation and bacterial infections.^{4,8-10}

Cardiovascular diseases (CVD/CVE) as defined by the World Health Organization (WHO),¹¹ are a group of disorders affecting the heart and blood vessels and could be divided into cardiovascular disease (CVD), including cerebrovascular disease, coronary heart disease (CHD), atherosclerotic cardiovascular disease (ACVD) and peripheral vascular disease (PVD), and cardiovascular events (CVE).¹¹ CVD, which is often asymptomatic, has the potential to result in acute CVE such as myocardial infarction (MI) and stroke, making it a prominent global cause of death.^{12,13} As human life expectancy continues to increase, the prevalence of chronic diseases, particularly CVD, also rises.¹² In 2019 CVD/CVE were globally the number one cause of death. Ischemic heart disease (IHD) was found to be the world's biggest killer, followed by stroke. Those two leading causes of death are accountable for 16% and 11% of all deaths respectively. Moreover, the fatal endings due to IHD is increasing since 2000.¹³

Periodontitis and CVD/CVE have some shared risk factors such as smoking, diabetes mellitus (DM), obesity, poor oral health and stress. ^{4,14} Given the high prevalence of periodontitis and CVD/CVE, as well as their shared risk factors, there is a growing interest in understanding the association between these two conditions. Numerous studies have shown the significant independent association between periodontitis and CVD/CVE. ^{9,10,15} There is even the suggestion of a two-way (bidirectional) relationship between periodontitis and CVD/CVE. ¹⁶ In more detail there is increasing evidence suggesting that periodontitis may be a risk factor for CVD/CVE, such as coronary artery disease, stroke, and MI. ¹⁵ However a causal relationship has yet to be proven. Recently Lavigne and Forrest ¹⁷ have published an umbrella review examining the possible causal relationship of periodontitis to CVD/CVE by investigating systematic reviews (SRs) determining if periodontal therapy lowers the risk of CVE. The result of their review confirms the existence of an association. However, there was insufficient evidence to satisfy the Bradford Hill criteria ¹⁸ and to state that there is also a causal relationship between CVD/CVE and periodontitis. ¹⁷

Despite the growing body of literature on the relationship between periodontitis and CVD/CVE, the evidence remains elusive, and the practical implication is unclear. Therefore, there appears to be a need for a comprehensive and critical appraisal of the available evidence concerning the association between periodontitis and CVD/CVE and in addition estimate the potential causal link between these two conditions. Accordingly, the aim of this study was to prepare a synthesis of SRs (meta-review) on the association of periodontitis and CVD/CVE.

METHODS

A protocol was developed a priori following initial discussion between the members of the research team. The preparation and presentation of this meta review is in accordance with the Joanna Briggs Institute (JBI) methodological guideline,¹⁹ the PRISMA guideline^{20,21} and the AMSTAR tool²² to ensure the methodological quality of the review process and improve the strength of reporting. This study is registered at the International Prospective Register of Systematic Reviews (PROSPERO) by number CRD42023444999. The Institutional Review Board of the Academic Centre for Dentistry Amsterdam (ACTA) also provided approval with the following number: 2022-74229.

Focused question

A review question was formulated utilizing the population, exposure, comparison, outcomes and study (PECOS)²³ framework as follows:

What associations can be identified between CVD/CVE in individuals with periodontitis as opposed to those without periodontitis, based on information gathered from existing SRs?

- Patients: humans ≥ 16 years old
- Exposure: patients with periodontitis
- Comparison: individuals without periodontitis
- Outcome: parameters of CVD/CVE
- Study design: SRs

Search strategy

As part of the search strategy, electronic databases, including MEDLINE-PubMed, and special collections of Cochrane-CENTRAL were systematically queried up to September 21, 2023. The structured search aimed to identify relevant SRs and meta-analyses that address the association of periodontal disease on CVD/CVE. The comprehensive search was designed by two reviewers (MGPS and DES) to include all SRs that answer the focused question. Table 1 provides more details regarding the search approach employed. Additionally, references cited in the included studies were screened for supplementary SRs and the PROSPERO database was checked for ongoing reviews. No further unpublished work or grey literature was sought.

Table 1

Search strategy used for MEDLINE-PubMed.

{[<exposure>] AND [<outcome>]}

<Exposure:>

 $<((\mbox{``Periodontitis''}[Mesh])\ \ \mbox{OR Periodontitis OR (periodontal disease)}\ \ \mbox{OR (periodontal disease)}\ \mbox{OR (periodon$

<Outcome:>

<(("cardiovascular diseases" [MesH]) OR (cardiovascular diseases) OR cardi OR (cardiac disease) OR stroke OR cerebro OR (cerebrovascular accident) OR stroke OR Atherosclerosis OR arthero* OR myocardial* OR (Myocardial ischemia) OR (myocardial disease) OR (chronic heart disease) OR (cardiovascular disease) OR cardio* OR (acute myocardial infarction) OR (coronary vascular disease) OR (peripheral arterial disease))>

AND

<(systematic review*) OR meta-analysis OR (meta-analysis) OR (umbrella review*)>

 $The \ asterisk \ (*) \ was \ used \ as \ a \ truncation \ symbol. \ The \ search \ strategy \ was \ customized \ according \ to \ the \ database \ being \ searched.$

Screening and selection

Duplicate papers were identified and removed before assessment of the SRs. Titles and, when available, abstracts of all SRs were screened. This was performed by three independent reviewers (MGPS, EJSW and LPMW) using the Rayyan web application. ^{24,25} Titles and abstracts of all studies were read in detail and categorized as included, excluded or undecided using the inclusion criteria. The reviewers were blinded from each other's results during the two-staged selection process. After the screening process the search was unblinded and disagreements concerning eligibility were identified by Rayyan. ^{24,25} Only when full agreement was reached between the three reviewers (MGPS, EJSW and LPMW) the paper was included. Discrepancies were discussed and resolved to reach consensus and in case of disagreement a following discussing with a fourth reviewer (DES) made the final decision. Full text papers were obtained, further assessed, and ultimately processed for data extraction when all the inclusion criteria were fulfilled. Updates of SRs were checked, and the latest version was selected.

Inclusion and exclusion criteria

Studies that evaluated the association between periodontitis and CVD/CVE relative to individuals without periodontitis as outcome variable were included. A full-text review of all the pertinent articles was completed utilizing the following detailed eligibility criteria:

- SRs with or without a meta-analysis.
- Full text publications available in English or Dutch.
- SRs of studies conducted in humans that had at least two groups of individuals:
 - Evaluating a group of patients with periodontitis of \geq 16 years old.
 - Evaluating a group of individuals without periodontitis of \geq 16 years old.
 - No restriction was applied for the definition and severity of periodontitis.
- Studies assessing CVD/CVE related outcomes as confirmed by any of the following:
 - CVD as defined by cerebrovascular disease, coronary heart disease (CHD), atherosclerotic cardiovascular disease (ACVD) and peripheral vascular disease (PVD).
 - As the terms peripheral artery disease (PAD) and PVD are often used interchangeably, for this review the parameter PAD was described along with PVD.²⁶
 - CVE as defined by stroke and myocardial infarction (MI).
- Data from a SR were taken into consideration if more than one original study contributed to the underlying evidence.

The exclusion criteria were as follows:

- Pregnancy
- Apical periodontitis
- Peri-implantitis
- DM or any other synonymous condition (such as metabolic diseases).
- CVD/CVE outcomes defined by surrogate markers, biomarkers, or antibody levels.
- CVD/CVE outcomes derivatives such as hypertension (HT), atrial fibrillation (AF), arterial stiffness and carotid artery calcification (CAC).
- Periodontitis defined only by number of teeth or tooth loss (TL).
- Studies that primarily focused on the effect of periodontal treatment.

Data Analysis

Assessment of heterogeneity

The heterogeneity across studies was detailed according to the following factors:

- Methodological: variability in review approach, risk of bias assessment and analysis performed (descriptive and/or meta-analysis).
- Clinical: subject characteristics, periodontitis details, CVD/CVE details.

Citation analysis

To ascertain potential overlap among the primary clinical studies within the included SRs, a citation matrix was constructed. This matrix aimed to compile a comprehensive list of unique studies.²⁷

Data extraction

The papers that passed the screening and selection process and fulfilled the inclusion criteria, were processed for data extraction. If studies examined a bi-directional relationship of periodontitis and CVD/CVE only those data were extracted that evaluated periodontitis as exposure variable and CVD/CVE as outcome. The included SRs were categorized into groups based on CVD/CVE outcomes as defined by the WHO, being parameters of CVD and CVE. This together with data extraction was performed by two independent reviewers (MGPS and LPMW) using a standardized data extraction form. Disagreements between the reviewers were solved by discussion. If disagreement persisted, a third reviewer (DES), was consulted. The following characteristics of the included studies were extracted: publication details, focused question, search results, number of included studies, details on CVD/CVE outcome and the conclusions from the original authors. Furthermore, the method of analysis, whether descriptive and/or involving meta-analysis, was also documented. From the available meta-analysis, the risk ratio (RR) or odds ratio (OR) and the corresponding 95% Confidence Interval (CI) and p-value were extracted for both random- and fixed-effects models. Additionally, statistical heterogeneity of the included meta-analysis was extracted from tests of heterogeneity such as I², Q, X² and Ri together with the respective p-values. When within an included SR subgroup analysis was performed for gender, age, smoking status, periodontitis severity and/or study region, the corresponding data was also extracted. When feasible subgroup analysis on these patient and study characteristics was carried out.

Data interpretation

As a guide for interpreting the magnitude of the association of the extracted RRs, values of 1.22, 1.86, and 3.00 were deemed indicative of small, medium, and large magnitudes, respectively. Additionally, the values of the ORs of 1.68, 3.47, and 6.71 were indicative of small, medium, and large magnitudes, respectively. Meta-analyses outcomes resulting in a p<0.05 were considered to be statistically significant. Tests of heterogeneity resulting in a p<0.1 was considered to be statistically significant. As a guide to evaluate the potential magnitude of inconsistency among primary studies, an I² statistic of 0%-40% may indicate negligible levels of heterogeneity, 30%-60% may suggest moderate heterogeneity, and 50%-90% may indicate substantial heterogeneity. Furthermore, an I2 statistic exceeding 75% was interpreted to indicate considerable heterogeneity.

Quality assessment

The risk of bias was estimated independently by two reviewers (MGPS and LPMW) rating the reporting and methodological quality of the included SRs and meta-analyses using a combination of items described by the PRISMA^{20,21} and the AMSTAR²² checklist.

A list of 27 items was evaluated, each aspect of the reporting and methodological quality item score list was given a rating of a plus (+) for informative description of the item at issue and a study design meeting the quality standard, was assigned. Plus-minus (±) was assigned if the item was incompletely described and minus (-) was used if the item was not described or unknown.³¹

For the quality assessment score individual items with a positive rating were summed to obtain an overall percentage score and a score of 100% was reached if all individual items received good ratings when these ratings were added together. As a guide to interpret the estimated risk of bias, a range of 0%-40% may indicate a high risk of bias, a range of 40%-60% may indicate a substantial risk of bias, a range of 60%-80% may indicate a moderate risk of bias, and a range of 80%-100% may indicate a low risk of bias. Only SRs that included a meta-analysis could achieve a full score of 100%.

Assessment of causality

Toevaluate potential causality, the Bradford Hill criteria were employed, which offers a framework to evaluate the strength of evidence supporting a causal relationship between periodontitis and CVD/CVE. The following nine criteria were assessed by two reviewers independently (MGPS and LPMW): strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Disagreements were resolved through additional discussion to reach consensus. If a disagreement persisted, the judgement of a third reviewer (DES) was decisive.

Grading the 'Body of Evidence'

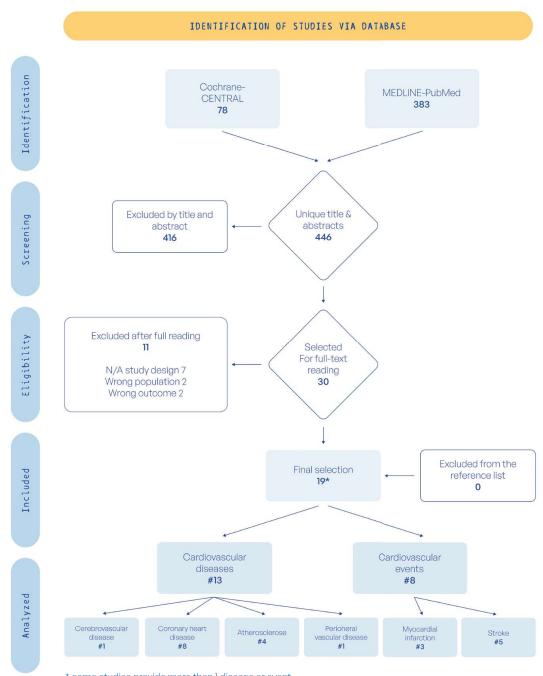
In this synthesis of SRs, the evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system³⁴ developed by the GRADE working group.^{35,36} The quality of the evidence was rated by two reviewers (MGPS and LPMW) as well as the strength of the recommendations according to the following aspects: study design, risk of bias, consistency and precision among outcomes, directness of results, detection of publication bias and magnitude of the association. Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, the judgement of a third reviewer (DES) was decisive.

RESULTS

Search and selection results

The search and selection process are illustrated in Figure 1. A total of 461 titles and abstracts were identified from the databases search of which 446 remained after duplicates were eliminated. There was a substantial interrater reliability between the three reviewers (Cohens kappa=0.62).³⁷ After screening titles and abstracts, a total of 30 full-text articles were selected for eligibility evaluation. Following a detailed review of these full texts, 11 studies were excluded due to issues related to study design, inappropriate population criteria, or irrelevant outcomes, as detailed in Online Appendix S1.

Figure 1
Search and selection results



^{*} some studies provide more than 1 disease or event

Consequently, 19 SRs, based on 173 primary clinical studies, were identified, and included in this review. An overview of the selected SRs with their IDs (I-XIX) and their characteristics is presented in Table 2. Of the final selection 13 SRs evaluated CVD, and eight studies evaluated CVE, of which one focused on cerebrovascular disease, eight on CHD, four on ACVD, one on PVD, six on stroke and three on MI.

Assessment of Heterogeneity

The 19 SRs analyzed in this synthesis demonstrated significant heterogeneity in various aspects, including the searched databases, characteristics of the original studies and their subjects, inclusion and exclusion criteria, the quality assessment scale employed, as well as the aims, methods of recording and reporting, and the inclusion of meta-analysis (Table 2).

Assessment of Citations

As presented in the citation matrix (Online Appendix S3), there was an overlap in the inclusion of primary clinical studies across multiple SRs, with some studies being included in more than one review.

Quality Assessment

The majority of the SRs evaluated in this synthesis were estimated to have a low to moderate risk of bias, as shown in Table 2 and Online Appendix S2. Two of the included reviews, VII³³ and VIII,³⁰ were found to exhibit a substantial risk of bias. The assessment was conducted through a critical evaluation of criteria, including the 'a priori' development and registration of a protocol, variety of searched databases or additional sources, inclusion of non-English literature, attempts to contact authors for additional information, grading of obtained evidence, and assessment of publication bias.

 Table 2

 Overview of the characteristics of the included SRs processed for data extraction.

Author (year) CVD/CVE Risk of Bias (%) (Online Appendix S2)	Data bases searched	Number of included studies/trails # involved participants base (end)	Leading mode of analysis	Original conclusions of review authors	Comments of the meta-review authors
I: Bahekar et al. 2007 ⁴⁰ CHD ROB: Moderate (63%)	MEDLINE-PubMed Cochrane- CENTRAL EMBASE CINAHL	15 studies ? (105324)	Meta- analysis	A possible association between periodontitis and CHD is found, as evidenced by a statistically significant increase in the incidence and prevalence of CHD among individuals with periodontal disease. Elevated levels of inflammatory mediators in patients with periodontitis suggest their role in atherothrombogenesis leading to CHD.	- There is considerable variation in the methods used to estimate periodontitis and OHD.
II: Blaizot et al. 2009 ⁴¹ CVD ROB: Low (81%)	 MEDLINE-PubMed Cochrane-CENTRAL EMBASE IILACS Pascal Biosis French Public Health Database 	32 studies ? (167931)	Meta- analysis	It seems from observational studies that subjects with periodontitis have higher odds and higher risk of developing CVD but the reduction in the risk of CVE associated with the treatment of periodontitis remains to be investigated.	 Three of the included studies used only tooth loss as a clinical exposure measurement related to periodontitis. The majority of the included studies are based on a population aged 40 years or older.
III: Dietrich et al. 2013 ⁴² ACVD ROB: Moderate (69%)	o Unknown	12 studies 25029 (?)	Descriptive analysis	The incidence of ACVD, as represented by incident CHD, cerebrovascular disease and PAD is higher in subjects with periodontitis and/or worse periodontal status, compared to subjects without periodontitis or with better periodontal status, independent of	 Some of the studies included in the analysis were based on the same study population, which raises the possibility of duplication of data, potential bias and overestimation of the results. Only descriptive analysis was performed.

many established cardiovascular risk factors. However, this may not be the case in all groups of the population.	E-PubMed II studies Meta- analysis AL Science ey Scholar	E-PubMed II studies Meta- The association between on the conjugate analysis periodontitis and CHD was found to studies used number of teeth on preliminary exploration of the effect of a reduced number of teeth on CHD. Although estimating having fewer teeth does not cardiovascular risk is still complicated in clinical work, the number of teeth is considered a risk number of teeth as an exposure variable. While periodontitis can lead to tooth loss, having fewer teeth does not necessarily mean that a person has periodontitis. Studies that used the number of teeth is considered a risk number of teeth as an exposure variable may not capture the full	independent one. extent of the relationship between periodontitis and CHD.
	MEDLINE-PubMed Cochrane- CENTRAL LILACS Web of Science Scopus OpenGrey Google Scholar	MEDLINE-PubMed Cochrane- CENTRAL EMBASE	
	IV: Fagundes et al. 2019 ⁴³ o Stroke o ROB: o Low (96%) o	V: Gao et al. 2021 ⁴⁴ CHD ROB: Low (81%)	

VII: Janket et al. 2003 ³⁸ CHD Stroke ROB: Substantial (52%)	0	MEDLINE-PubMed	9 studies Only cohort studies 107011 (7035)	Meta- analysis	periodontitis is associated with the increased risk of development of subsequent CVD/CVE by approximately 19% in the general population. However, this summary result might still underestimate the true risk increase. Because in some studies inadequate confounding adjustment resulted in an overestimate of the RR by 12.9% and use of questionnaires resulted in an underestimate of the RR by 29.7%, the net result is still lower than the true RR.	- The predictor variable, periodontitis, was defined as gingivitis or periodontitis. It was not clear if gingivitis was included in the metaanalysis.
VIII: Khader et al. 2004³³ Cerebrovascular disease CHD ROB: Substantial (59%)	0	MEDLINE-PubMed	11 studies ? (104710)	Meta- analysis	Findings indicate that periodontal infection increases the risk of CHD and cerebrovascular disease. However, this meta-analysis provided no evidence for the existence of strong associations between periodontitis and CHD and cerebrovascular disease.	 Three included studies indicated periodontitis on self-reported evaluation. Three included studies are solely based on a population of men.
IX: Lafon et al. 2014 ⁴⁶ Stroke ROB: Moderate (70%)	0 0 0 0	MEDLINE-PubMed Cochrane- CENTRAL EMBASE ISI Web of Science	9 studies Only cohort studies 138930 (?)	Meta- analysis	Our results are in accordance with those of previous reviews suggesting a link between stroke and periodontitis. Pooled data were calculated based on results from cohort studies with various quality scores. More epidemiological and clinical studies are thus needed to clarify the relationship between these inflammatory diseases.	 Only four of the nine included studies performed simple or complete clinical screening to indicate periodontitis evaluation. The remaining studies determined this from a questionnaire or the number of teeth. Three studies were included in which the patients were known to have a CVD/CVE history. Four studies are based on men only. The ages of the populations are not given.

X: Larvin et al. 2020 ⁴⁷ CVD CHD Stroke MI ROB: Low (85%)	0 0 0	MEDLINE-PubMed Cochrane- CENTRAL EMBASE	30 studies Only RCT and cohort studies ? (10007700)	analysis	The results of this SR and meta- analysis demonstrate increased risk of CVD/CVE in people with periodontitis. Males and people with severe periodontitis have the highest risk of developing cardiovascular diseases indicating possible target populations for future public health interventions and screening.	 Since 21 studies having a critical risk of bias and 11 having a serious risk of bias, it may be suggested that the overall quality of evidence may be lower than desired. The significant risk of publication bias demonstrated in the funnel plot and Egger's test indicates that the study may have included only a subset of relevant studies, potentially leading to an overestimation or underestimation of the true effect size. Nine included studies indicated periodontitis on self-reported
XI: Leira et al. 2017 ⁴⁸ Stroke ROB: Low (89%)	0 0 0 0	MEDLINE-PubMed EMBASE Web of Science Current Contents Connect	8 studies ? (14091)	Meta- analysis Descriptive analysis	Our results for cohort studies, which are less prone to bias than case-controls studies, together with the results of high-quality studies, show that antecedents of periodontitis may be a moderate to strong risk factor of ischemic stroke.	- No potential confounding factors that could affect the association between periodontitis and ischemic stroke were analyzed, which could limit the generalizability of the findings.
XII: Meregildo- Rodriguez et al. 2022* CHD ROB: Low (85%)	0 0 0 0 0	MEDLINE-PubMed EMBASE Web of Science Scopus Science Direct Google Scholar	46 studies ? (6806286)	analysis	This study shows that periodontitis would be a non-traditional risk factor for developing ACS. The results support the hypothesis that chronic inflammation caused by periodontitis is involved in the pathogenesis of ACVD and ACS. Given the high prevalence of periodontitis in the population, this would have a profound impact on public health, health policy and clinical specialties, such as cardiology and neurology. Therefore, maintaining adequate periodontal	 Four included studies indicated periodontitis on self-reported evaluation. Seven studies are based on men only and three studies on woman only. The significant risk of publication bias demonstrated in the funnel plot indicates that the study may have included only a subset of relevant studies, potentially leading to an overestimation or underestimation of the true effect size.

				health could be an effective measure to reduce the risk of ACS. However, our results should be taken with caution due to the quality of the evidence and the heterogeneity of the studies.	
XIII: Orlandi et al. 2014 ⁵⁰ ACVD ROB: Low (91%)	MEDLINE-PubMed Cochrane- CENTRAL EMBASE UILACS SCI-EXPANDED	35 studies	Meta- analysis Descriptive analysis	periodontitis is associated with greater subclinical ACVD as assessed by increased c-IMT and FMD.	- A high level of heterogeneity was observed in both case-control and intervention trials, indicating differences in research protocols and clinical heterogeneity that may affect the robustness of the findings. However, the statistical heterogeneity was low.
XIV: Qin et al. 2021 ⁵¹ MI ROB: Moderate (74%)	MEDLINE-PubMed EMBASE The Cochrane Library	10 studies Only cohort studies ? (5369235)	Meta- analysis	periodontitis is modestly associated with MI risk, especially in women.	- After subgrouping, there was still a significant level of heterogeneity present in the meta-analysis.
XV: Sfyroeras et al. 2012 ⁵² Stroke ROB: Moderate (63%)	o MEDLINE-PubMed	13 studies ? (123229)	Meta- analysis	There is evidence that periodontitis is associated with increased risk of stroke. However, the results of this meta-analysis should be interpreted with caution because of the heterogeneity of the studies as well as the differences in periodontitis definition.	 Patients with ischemic and hemorrhagic stroke were both included, however separate statistical analyses were not able to be conducted. Of the 13 included studies, six prospective studies compared individuals with periodontitis to those without. The other studies evaluated the incidence of periodontitis in individuals with CVD/CVE to those without.
XVI: Voinescu et al. 2019 ⁶³	MEDLINE-PubMedScopusScience DirectGoogle Scholar	17 studies ?	Descriptive analysis	The prevalence of periodontitis in patients with ischemic cardiac disease is high, the existence of a correlation between the two	 Description of study characteristics of the included studies are limited. Only descriptive analysis was performed.

ROB: Moderate (63%)				pathogens being most often established in studies, although the mechanism has not been elucidated yet.	
XVII: Wang et al. 2019 ⁵⁴	MEDLINE-PubMed Cochrane-	25 studies	Meta- analysis	The meta-analysis of 25 studies identified by comprehensive SR	- Two of the included studies used only tooth loss as a clinical exposure
		? (22090)	`	indicates that periodontitis is an	measurement related to
ACVD	o EMBASE			independent risk factor for both	periodontitis and one study based
PVD (PAD)	o Google Scholar			CAD and LEAD.	the periodontitis exposure on self-
	 Ovid Medline 				reported periodontal assessment.
ROB:					- Population information other than
Moderate (74%)					location of the studies was not given.
XVIII: Xu et al.	MEDLINE-PubMed	22 studies	Meta-	The meta-analysis yielded a	- Of the 22 included studies, three
2017 ⁵⁵	o EMBASE		analysis	statistically significant association	cohort studies compared individuals
	o The Cochrane	? (129630)		between periodontitis and MI.	with periodontitis to those without.
₹	Library			Subgroup analyses also confirmed	The other studies evaluated the
				the elevated risk for MI in	periodontal health in individuals with
ROB:				periodontitis subjects, although	MI history compared to those
Low (81%)				heterogeneity should be noted.	without MI history.
XIX: Zeng et al.	 MEDLINE-PubMed 	15 studies	Meta-	Our meta-analysis of 15	- The association between
2015%	o EMBASE		analysis	observational studies indicates that	periodontitis and CAD may be
		? (17330)		periodontitis was associated with	confounded by smoking and DM,
ACVD				carotid ACVD, although currently	since six of the included studies did
				available evidence is insufficient to	not take these factors into account
ROB:				confirm the causal relationship of	while analyzing the relationship
Moderate (70%)				periodontitis and carotid ACVD.	between periodontitis and CAD.
					Adjusting for these factors may
					weaken the observed relationship.

Abbreviations: ?, Is not reported/unknown; AOS, acute coronary syndrome; ACVD, Atherosclerotic cardiovascular disease; CAD, Carotid atherosclerosis; CAD, Coronary heart disease; c-IMT, Carotid intima media thickness; CVD, Cardiovascular event; FMD, Flow mediated dilatation; GRADE, Grading of recommendations assessment, development, and evaluation; IHD, Ischemic heart disease; LEAD, Peripheral artery disease; PVD, Peripheral vascular disease; RR, Relative risk; SR, Systematic review.

Study outcome results

The analysis was performed per category CVD and CVE. For a detailed analysis on the different outcome aspects see Online Appendix S4.

CVD

13 SRs (I,⁴⁰ II,⁴¹ III,⁴² V,⁴⁴ VI,⁴⁵ VII,³⁸ VIII,³⁹ X,⁴⁷ XII,⁴⁹ XIII,⁵⁰ XVI,⁵³ XVII⁵⁷ and XIX⁵⁶) were identified evaluating the relationship between periodontitis and CVD. Details and an overview of the extracted meta-analysis data of the included SRs are shown in Table 3A and Table 4A. Most of the studies further specified CVD as cerebrovascular disease, CHD, ACDV or PVD. Two SRs (II and X) performed a meta-analysis for CVD specifically and showed a significant association of periodontitis and CVD, for patients with periodontitis as compared to those without. The OR and RR, magnitude of the association of these were estimated to be negligible to small (Table 3A). The heterogeneity among the clinical studies in the meta-analysis is estimated to range from potentially not significant to considerable (Table 3A).

Cerebrovascular disease

One SR (VIII³⁹) was identified which evaluated the association between periodontitis and cerebrovascular disease. The results of the performed meta-analyses showed a significantly increased risk of cerebrovascular disease for patients with periodontitis in comparison to individuals without periodontitis. As shown in Table 3A, the interpretation of the values of the extracted RR, indicates that the magnitude of the association can be considered as negligible. The statistical heterogeneity associated with the meta-analysis is not described in this SR (Table 3A).

CHD

Eight SRs (I,⁴⁰ V,⁴⁴ VI,⁴⁵ VII,³⁸ VIII,³⁹ X,⁴⁷ XII⁴⁹ and XVI⁵³) were identified, examining the association between periodontitis and CHD. All these reviews revealed a significant relationship, indicating an elevated risk of CHD for patients with periodontitis compared to those without. Interpretation of the ORs and RRs is detailed in Table 3A, suggesting that the magnitude of the association can be estimated to range from negligible to medium. Based on the findings of the meta-analyses, it appears that the statistical heterogeneity among the included clinical studies ranges from potentially not important to considerable (Table 3A).

ACVD

Four SRs (III,⁴² XIII,⁵⁰ XVII⁵⁷ and XIX⁵⁶) were identified which evaluated the association of periodontitis and ACVD. All studies showed a significant relationship, with an increased risk for patients with periodontitis compared to those without. However, the range of the ORs implies that the value of the association is estimated to range from negligible to small. The meta-analyses indicate that the heterogeneity among the clinical studies ranges from potentially not important to considerable (Table 3A).

PVD

A single SR (XVII⁵⁷) was identified assessing the association between periodontitis and PAD of which the results indicate a significantly heightened risk for patients with periodontitis in developing PAD. However, upon interpreting the OR, the actual magnitude of the association is estimated to be negligible (Table 3A). Based on the meta-analysis the statistical heterogeneity was also considerable among the included studies (Table 3A).

CVE

Eight SRs (IV,⁴³ VII,³⁸ IX,⁴⁶ X,⁴⁷ XI,⁵⁵ XIV,⁵¹ XV⁵² and XVIII⁴¹) were identified evaluating the association between periodontitis and CVE. Details and an overview of the extracted data of the meta-analysis of the included SRs are shown in Table 3A and Table 4B. All studies further specified CVE as stroke or MI.

Stroke

Six SRs (IV, 43 VII, 38 IX, 46 X, 47 XI 48 and XV 52) were identified which evaluated the association of periodontitis and stroke. All studies showed a significant relationship, with an increased risk for patients with periodontitis compared to those without. The interpretation of the extracted ORs and RRs (for details see Table 3A) shows that the magnitude of the association ranges from none to large. As emerging from the meta-analyses, the heterogeneity among the included clinical studies ranges from potentially not important to considerable (Table 3A).

ΜI

Three SRs (X,⁴⁷ XIV⁵¹ and XVIII⁵⁵) were identified which evaluated the relationship between periodontitis and MI of which the results suggest an association between periodontitis and the risk of MI. However, the interpretation of the association indicated that the magnitude of the ORs could be considered as negligible (Table 3A). The statistical heterogeneity among the clinical studies ranges from substantial to considerable (Table 3A).

Subgroup analysis

Nine SRs (II,⁴¹ III,⁴² VI,⁴⁵ VII,³⁸ X,⁴⁷ XII,⁴⁹ XIV,⁵¹ XVI⁵³ and XIX⁵⁶), performed sub-analysis evaluating the association of periodontitis and CVD/CVE relative to parameters for gender, age, smoking status, periodontitis severity or study region. Details and an overview of the extracted data of the meta-analyses for these subgroups in the included SRs are shown in Table 3B.

Gender

Five SRs (III,⁴² VI,⁴⁵ X,⁴⁷ XII⁴⁹ and XIV⁵¹) evaluated the association of periodontitis and CVD/CVE in relation to gender. Three SRs suggested a higher risk of CVD/CVE in women with periodontitis (VI, XII and XIX) while a greater risk was observed in men according one SR (III). The observed differences between genders were not statistically significant and the estimation of the magnitude of the association based on ORs and RRs values ranges from none to small (Table 3B). As indicated by the meta-analysis the heterogeneity among the included clinical studies is in the range from potentially not important to considerable (Table 3B). Consequently, the association between periodontitis and CVD/CVE in relation to gender remains inconclusive.

Age

Three SRs (II,⁴¹ III⁴² and VII³⁸) evaluated the association of periodontitis and CVD/CVE relative to age. The findings suggest that age may play a role in the association between periodontitis and CVD/CVE, with younger age groups (\leq 65 years old) experiencing a potentially higher risk. The observed OR from one meta-analysis (VII) suggest that the magnitude of the association is considered small (Table 3B). No information was provided on statistical heterogeneity in the meta-analysis.

Periodontitis severity

Four SRs (III,⁴² X,⁴⁷ XVI⁵³ and XIX⁵⁶) evaluated the association of periodontitis and CVD/CVE in relation to periodontitis severity. The findings suggest that periodontitis severity may play a role in the association between periodontitis and CVD/CVE, with individuals with severe periodontitis experiencing a significantly higher risk. Based on the interpretation of the ORs and RRs, the magnitude of the association was estimated to range from negligible to small (Table 3B). The statistical heterogeneity as emerging form the meta-analysis ranges from potentially not important to considerable among the included clinical studies (Table 3B).

Smoking status

Two SRs (III⁴² and XVI⁵³) evaluated the association of periodontitis and CVD/CVE relative to the smoking status. The association between periodontitis and CVD/CVE parameters in relation to smoking status remains inconclusive as conclusions of both SRs were based on limited evidence from a single clinical study. Assessment of heterogeneity with one included study was not applicable.

Study region

Three SRs (II,⁴¹ X⁴⁷ and XII⁴⁹) evaluated the association of periodontitis and CVD/CVE in relation to the region where the clinical study was performed. The findings suggest that the region may influence the association between periodontitis and CVD/CVE, with only one SR (XII) reporting this difference as statistically significant. Additionally, the interpretation of the extracted ORs and RRs indicates that the magnitude of the association ranges from none to medium (Table 3B). The meta-analysis revealed that among the included clinical studies, heterogeneity ranged from potentially negligible to considerable (Table 3B).

Table 3A

Overview of data extraction of the included SRs.

Source				Outcome			Heterogeneity	
Disease or event	SR	No. studies in meta- analysis (variable)	No. patients in meta- analysis	Effect model (Fixed/ Random): OR/ RR*	95% CI	p value	l², Q*, X²**, Ri***	p value
		32 (total)	167931	NR	NR	NR	NR	NR
	141	7 (cohort)	147821	Fixed: 1.34*	1.27–1.42	<0.0001	5.6%	0.39
CVD		22 (cs & cc)	20110	Random: 2.35	1.87–2.96	<0.0001	49.9%	0.0044
	747	30 (total)	10007700	NR	NR	NR	NR	NR
	: <	26 (CVD)	9491880	Random: 1.20*	1.14–1.28	sig	98.1%	0.00
Cerebrovascular	1 /11130	6 (total)	36915	Random: 1.13*	1.01–1.27	0.032	5	خ
disease	5 = >	4 (cohort)	33744	Random: 1.11*	0.98-1.25	0.106	خ	c·
		15 (total)	105324	NR	NR	NR	NR	NR
	140	5 (cohort)	86092	Fixed:1.14*	1.07–1.21	<0.001	homog	not sig
	<u> </u>	5 (cs)	17809	Fixed: 1.59	1.33–1.91	<0.001	homog	not sign
		5 (00)	1423	Fixed: 2.22	1.59–3.12	<0.001	homog	not sign
		II (total)	284622	NR	N.S.	N. N.	NR	NR
	V ⁴⁴	10 (periodontitis vs non- periodontitis)	175795	Fixed: 1.18	1.10–1.26	Sig	11.7%	0.330
	VI45	6 (total)	33163	Random: 1.22*	1.01–1.51	sig	13.03*	0.048
4	VII38	9 (total, CHD)	7035	Random: 1.19*	1.08-1.32	0.000	23.624*	0.003
CHD		8 (total)	94096	Random: 1.15*	1.06–1.25	0.001	homog**	0.472
	VIII39	6 (cohort)	85693	Random:1.14*	1.04–1.25	0.004	3	5
		3 (cohort, fatal)	7776	Random: 1.20*	0.90–1.60	0.205	3	5
	X ⁴⁷	13 (CHD)	3332392	Random: 1.14*	1.08–1.21	sig	68.4%	0.00
		46 (total)	6806286	Random: 1.35	1.25–1.45	<0.00001	86%	<0.00001
	VII49	17 (cohort)	6787657	Random: 1.13	1.05–1.21	0.0010	81%	<0.00001
	=	4 (cs)	9056	Random: 1.67	0.79-3.50	0.18	46%	0.13
		25 (cc)	9573	Random: 2.62	2.05-3.35	<0.00001	86%	<0.00001
	XVI ⁵³	NA	NA	NA	ΥZ	ΑN	ΑN	ΑN
	III ⁴²	NA	ΑN	ΥN	ΥZ	ΑN	ΥZ	NA
		22 (total)	6034	NR	NR	NR	NR	NR
ACVD.	XIII50	16 (C-IMT)	5452	AN	NA	<0.0001	0.0%	0.922
		6 (FMD)	582	NA	ΑN	<0.001	80.1%	0.000
	XVII ⁵⁴	9 (LEAD)	4468	Random: 3.00	2.23-4.04	<0.001	0.0%	0.563
	XIX56	15 (total)	17330	Random: 1.27	1.14–1.41	<0.01	78.9%	<0.01

		10 (periodontitis vs non-	3961	Random: 1.75	1.33–2.30	<0.01	74.64%	<0.01
		periodoriuis)		-	6			0
(טעט) טעס	Y1/1154	25 (total)	22090	Random: 1.60	1.41–1.82	<0.001	80.5%	0.000
	= ^ <	16 (CAD)	18902	Random: 1.39	1.24–1.56	<0.001	79.4%	0.000
		ll (total)	32213	NR	N.	N. N.	N N	Z
	IV 743	3 (cohort)	28900	Random: 1.88*	1.55–2.28	<0.00001	%0	0.59
	<u> </u>	7 (00)	1513	Random: 2.31	1.39–3.84	0.001	77%	0.0003
		4 (cc, ischemic stroke)	1015	Random: 2.72	2.00–3.71	<0.00001	4%	0.37
	v /II38	2 (stroke)	1010	Random: 2.85*	1.78–4.56	0.000	خ	5
	ΙΛ	5 (fatal)	4733	Random: 1.54*	1.10-2.17	0.012	خ	5
	X ₄₇	18 (stroke)	3651223	Random:1.24 [⋆]	1.12–1.38	sig	95.5%	0.00
	17.46	9 (total)	138930	NR	NR	NR	NR	NR
	<u>~</u>	4 (periodontitis outcomes)	27730	Random: 1.63*	1.25–2.00	sig	homog	NR
		: : : : : : : : : : : : : : : : : : : :		Fixed: 1.07*	1.03–1.11	•	- - - (0
Stroke		8 (total)	14091	Random: 2.88*	1.53-5.41	Sig	***0.1	0.000.0
		1	, NOOL	Fixed: 2.52*	1.77–3.58		* * * *	C
		s (conort)	12240	Random: 2.52*	1.77–3.58	Sig	I.U	0.50
	× 148	(())	0.00	Fixed: 1.06*	1.02–1.10		****	5000
	<u>!</u>	(22) 6	1840	Random: 3.04*	1.10-8.43	Dis.	0.0	0.000.0
		(0):2:+0;+17;-2 dxid) +	0321	Fixed: 4.83*	3.13–7.46		* * * * *	7
		4 (mgn quality studies)	06/1	Random: 4.83*	3.13–7.46	Sig	0.0	74.0
		:	()	Fixed: 1.06*	1.02–1.10		***	70000
		4 (Iow quality studies)	12341	Random: 2.02*	1.06–3.85	Sig	0.1	1.0000.0
	V 167	13 (total)	123229	NR	NR	NR	NR	N N
	~ ^ ~	6 (prospective studies)	105247	Random: 1.47*	1.13–1.92	0.0036	heterog	sig
	X ⁴⁷	(IM)	771925	Random: 1.12*	0.96–1.30	not sig	82.9%	00:00
	VV /III55	22 (total)	129630	NR	NR	NR	NR	NR
Σ	\ \	4 (cohort)	47819	Random: 1.18	0.98-1.42	not sig	64.8%	0.036
		10 (total)	5369235	Random: 1.13	1.04-1.21	0.004	78%	0.000
	XIV ⁵¹	5 (high quality studies)	5270520	Random: 1.20	1.03-1.37	0.019	86.5%	0.000
		5 (moderate quality studies)	98715	Random: 1.09	0.94–1.24	0.254	64.1%	0.025

Table 3B

Overview of data extraction of the included SRs for subgroup analysis.

Source				Outcome			Heterogeneity	
Subgroup analysis	SR	No. studies in meta-analysis (variable)	No. patients in meta- analysis	Effect model (Fixed/ Random): OR/ RR*	95% CI	p value	l², Q*, X²**, Ri***	p value
	III ⁴²	A'N	ΑN	AN	Ϋ́Z	NA	AN	AN
		? (combined)	خ	Random:1.31*	1.08–1.59	not sig	¿.	خ
	VI ⁴⁵	? (women)	ز	Random: 1.59*	1.28–1.96	خ	۲	خ
		? (men)	ċ	Random: 1.23*	0.92–1.64	ċ	C+	ċ
		16 (combined)	6467175	Random: 1.04*	0.92–1.17	not sig	90.7%	0.00
	X ⁴⁷	6 (women)	1691927	Random: 1.11*	1.02–1.22	ż	85.8%	0.00
Gender		14 (men)	4775248	Random: 1.16*	1.08–1.25	ż	%9.96	0.00
		37 (combined)	6714856	Random: 1.35	1.24–1.45	0.67	86%	<0.00001
	XIII49	2 (woman)	40056	Random: 1.96	0.62–6.17	0.25	87%	0.005
		7 (men)	51374	Random: 1.48	1.11–1.97	0.007	%19	0.02
		NR (combined)	NR	NR	NR	NR	NR	NR
	XIV	1 (women)	39863	Random: 1.39	1.17–1.65	0.000	NA	AN
		3 (men)	498053	Random: 1.05	0.89–1.24	0.560	18.0%	0.300
	1141	? (cohort, mean age)	5	5	3	0.06	S	ż
000	=	? (cs, cc, mean age)	5	5	5	0.11	Ċ	3
ש פרי	11142	NA	AN	AN	Ϋ́Z	ΑN	ΥZ	∀Z
	VII38	6 (≤ 65 years)	2890	Random: 1.44*	1.20–1.73	0.000	23.624*	0.003
	11142	NA	NA	NA	AN	NA	NA	AN
		18 (combined)	7016015	Random: 1.20*	1.15–1.25	?	90.5%	0.00
		18 (severe vs mild)	4724176	Random: 1.11*	1.00–1.22	sig	?	5
	X ₄₇	18 (severe)	2165275	Random: 1.25*	1.15–1.35	?	71.6%	0.00
		15 (moderate)	2291839	Random: 1.23*	1.14–1.32	ż	70.6%	0.00
Periodonina severity		12 (mild)	2558901	Random: 1.09*	1.05–1.14	ż	80.0%	0.00
	XVI53	NA	NA	NA	ΥN	NA	AN	AN
		NR (combined)	NR	NR	NR	NR	NR	NR
	X X X 200	5 (severe)	13369	Fixed: 1.14	1.06–1.23	<0.01	47.16%	0.11
		4 (moderate)	13166	Fixed: 1.10	1.04–1.16	<0.01	%0	0.9
Smoking status	11142	NA	NA	NA	∀Z	AN	ΑN	A A

? (cohort, North America)	AN ?	NA Fixed: 1.50*	NA 1.34–1.68	AN 000	AN c	AZ c
? (cohort, China)		Fixed: 1.28*	1.17–1.44	90:0	٠.	
? (cs, cc, Europe)	? Rando	Random: 3.95	2.54–6.15			
? (cs, cc, South America)	? Rando	Random: 2.34	1.48–3.70	0	c	C
? (cs, cc, North America)	? Rando	Random: 2.02	1.49–2.73	00:00		٠.
? (cs, cc, Scandinavia)	? Rando	Random: 2.00	1.27–3.15			
30 (combined)	10007700 Randor	Random: 1.20*	1.14–1.26	c.	97.3%	0.00
4 (Europe)	134035 Randor	Random: 1.36*	1.20-1.54	Ċ	71.3%	0.00
16 (North America)	835583 Rando	Random: 1.15*	1.09–1.26	خ	80.3%	0.00
10 (Asia/ Australia)	9038082 Randor	Random: 1.20*	1.11–1.30	¢.	98.1%	0.00
4 (Europe vs Asia/ Australia)	9172117 Rando	Random: 1.18*	1.03-1.35	c.	Ċ	~
16 (Europe vs North America)	969618 Randor	Random: 1.03*	0.93-1.13	خ	Ċ	٠.
46 (combined)	6806286 Rando	Random: 1.35	1.25–1.45	<0.00001	%98	<0.00001
13 (North America)	134107 Rando	Random: 1.30	1.16–1.46	<0.00001	67%	0.00003
4 (South America)	920 Rando	Random: 4.43	2.39-8.23	<0.00001	%0	0.95
20 (Europe)	126163 Rando	Random: 1.92	1.59-2.31	<0.00001	84%	<0.00001
9 (Asia)	6545096 Rando	Random: 1.09	0.96–1.25	0.20	%98	<0.00001

thickness; Os, cross-sectional study; OVD, Cardiovascular disease; OVE, Cardiovascular event; FMD, Flow mediated dilatation; Heterogeneous; Homogeneous; LEAD, Peripheral artery disease; NA, not applicable; NR, Not reported; MI, Myocardial infarction; OR, Odds Ratio; PAD, Peripheral artery disease; PVD, Peripheral vascular disease; Q*, Cochran's Q test for heterogeneity; Ri**, DerSimonian and Laird Q test for heterogeneity; RR, Relative Risk; Sig; significant; SR, Systematic review; X***, Chi-square test for heterogeneity. Abbreviations: ?, Is not reported/unknown; ACVD, Atherosclerotic cardiovascular disease; CAD, Carotid atherosclerosis; CHD, Coronary heart disease; Co, case-control study; c-IMT, Carotid intima media

Legends table 3a and 3b

Large RR 3.00
Medium RR 1.86
Small RR 1.22
None RR 0
Meta-analysis outcome (RR)

As a guideline, the effect sizes of the RR were interpreted using a normal standard deviate. Effect sizes of 1.22, 1.86, and 3.00 were considered indicative of small, medium, and large magnitudes, respectively 28.

Large OR 6.71
Medium OR 3.47
Small OR 1.68
None OR 0
Meta-analysis outcome (OR)

As a guideline, the effect sizes of the OR were interpreted using a normal standard deviate. Effect sizes of 1.68, 3.47, and 6.71 were considered indicative of small, medium, and large magnitudes, respectively 29.

Significant	Meta-analyses outcomes: p<0.05	
Not significant	Meta-analyses outcomes: p≥0.05	
Significance	(d)	

Meta-analyses outcomes resulting in a p<0.05 was considered to be statistically significant.

ntial Considerable 75-100%
Substantial 50-90%
Moderate 30-60%
Potential not important 0-40%
Test of heterogeneity (I²)

As a guideline, to assess the potential magnitude of inconsistency between studies, an P statistic of 0%-40% may represent unimportant levels of heterogeneity, 30%-60% may represent moderate heterogeneity, 50%-90% may represent substantial heterogeneity. An I2 statistic of greater than 75% was interpreted to indicate considerable heterogeneity 30.

Table 4ASummary of the effect sizes of the extracted RRs and ORs for CVD.

CVD						
	Total number	Number of performed	Effect size of	the extracted	RRs ²⁸ and ORs	29
SR	of included studies	meta- analysis	None	Small	Medium	Large
 40	15	3	2/3	1/3		
41	32	2		2/2		
42	12	0		N	IA	
V ⁴⁴	11	1	1/1			
VI ⁴⁵	7	1	1/1			
VII ³⁸	9	1	1/1			
VIII ³⁹	11	5	5/5			
X ⁴⁷	30	2	2/2			
XII ⁴⁹	46	4	3/4 1/4			
XIII ⁵⁰	35	3	3/3			
XVI ⁵³	17	0	NA			
XVII ⁵⁷	25	3	2/3 1/3			
XIX ⁵⁶	15	2	1/2 1/2			
Summary		27	8.1/11=			0/11= 0%
Overall		Of the 11 SRs t the values of F magnitude of	Rs and ORs a	re considered	to show a neg	

Abbreviations: CVD, Cardiovascular disease; NA, not applicable (no meta-analysis available); OR, odds Ratio; RR, relative risk; SR, Systematic review.

Table 4BSummary of the effect sizes of the extracted RRs and ORs for CVE.

CVE						
	Total number	Number of performed	Effect size of	the extracted f	RRs ²⁸ and ORs	29
SR	of included studies	meta- analysis	None	Small	Medium	Large
IV ⁴³	11	3		2/3	1/3	
VII_{38}	9	2		1/2	1/2	
IX ⁴⁶	9	1	1/1			
X ⁴⁷	30	2	2 1/2 1/2			
XI ⁴⁸	8					3/10
XIV^{51}	10	3	3/3			
XV ⁵²	13]		1/1		
XVIII ⁵⁵	22	1	1/1			
Summary	Summary 23				0.3/8=	
			35%	46%	15%	4%
Overall		Of the 8 SRs, t the values of R of the associa	RRs and ORs a	re considered		* ` '

Abbreviations: CVE, Cardiovascular event; NA, not applicable (no meta-analysis available); OR, odds Ratio; Periodontal disease; RR, relative risk; SR, Systematic review.

Assessment of causality

The application of the Bradford Hill criteria¹⁸ as summarized in Table 5 and Online Appendix S5 shows the detailed analysis. Three out of the nine criteria, namely consistency, biological gradient, and plausibility, can be satisfied. Regarding the causality of the association between periodontitis and CVD and CVE it is important to recognize that definitive establishment of causality cannot be inferred solely from the findings of the current synthesis.

Evidence profile

The strength of the body of evidence based on GRADE^{34,35} are summarized in Table 6. With respect to the relationship of periodontitis and parameters of CVD/CVE there is moderate certainty that the magnitude of this association can be estimated as negligible to small, and causality, according to Bradford Hill criteria, remains undefined.

Table 5Overview of the Bradford Hill criteria¹⁸ for causality.⁵⁸

Ouitouis	Maning	C	VD	С	VE
Criteria	Meaning	Yes	No	Yes	No
Strength of association (Table 3)	A strong association is more likely to have a causal component than a modest association. Strength of the association is determined by the types of existing studies. The highest-level studies from the evidence pyramid would represent the strongest associations (i.e., RCTs and SRs with meta-analyses). Results from these studies must demonstrate an OR or RR of at least 2.0 or above in order to be meaningful. Anything between 1 and 2 is weak while >2 is moderate and >4 is considered strong.		x		×
Consistency	A relationship is repeatedly observed in all available studies.	х		х	
Specificity	A factor influences specifically a particular outcome or population. The more specific an association between a factor and an effect, the greater the probability that it is causal.		x		X
Temporality	The cause must precede the outcome it is assumed to affect (e.g., smoking before the appearance of lung cancer). Outcome measured over time (longitudinal study).		x		Х
Biological gradient (dose- response)	The outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory (e.g., the more cigarettes one smokes, the greater the chance of the cancer occurring).	x		x	
Plausibility	The observed association can be plausibly explained by substantive matter (i.e., biologically possible).	х		х	
Coherence	A causal conclusion should not fundamentally contradict present substantive knowledge. Studies must not contradict each other.		х		х
Experiment	Causation is more likely if evidence is based on randomized experiments or a SR of randomized experiments. However, RCTs may not be ethically possible and thus prospective rather than experimental studies, such as cohort studies, may be the highest level of evidence available.		x		х
Analogy	For analogous exposures & outcomes an effect has already been shown (e.g., Effects first demonstrated on animals or an effect previously occurring on humans such as the effects of thalidomide on a fetus during pregnancy).		x		x

Abbreviations: CVD, Cardiovascular disease; CVE, Cardiovascular event; OR, Odds ratio; RCT, Randomized controlled trial; RR, Relative risk; SR, Systematic review.

Table 6Estimated evidence profile (GRADE)³⁴ for the effect of periodontitis on various cardiovascular parameters.

GRADE	CVD	CVE
Study designs	SRs N=13	SRs N=8
Reporting and methodological estimated potential risk of bias (Table 5)	Low to substantial	Low to substantial
Consistency	Rather consistent	Rather consistent
Heterogeneity (Table 2)	Rather heterogeneous	Rather heterogeneous
Directness	Rather indirect Rather direc	
Precision	Rather precise Rather precis	
Publication bias	Possible	Possible
Magnitude of the effect (Table 4) ^{28,29}	Negligible	Negligible to Small
Certainty	Moderate Moderate	
Bradford Hill criteria ¹⁸	Uncertain causal relationship	Uncertain causal relationship
Summary and direction of the findings	Regarding the association betw CVD/CVE, there is a moderate I magnitude is negligible to small	level of certainty that the

Abbreviations: CVD, Cardiovascular disease; CVE, Cardiovascular event; periodontitis; SR, Systematic review.

DISCUSSION

Summary of the findings

This synthesis aimed to summarize the existent dental and medical evidence from SRs concerning the association of periodontitis and parameters of CVD/CVE. Specifically, SRs were included due to their comprehensive nature and ability to provide a stronger body of evidence compared to individual clinical studies. The analysis of the 19 SRs included in this synthesis consistently demonstrated an increased risk of CVD and CVE in patients with periodontitis compared to individuals without periodontitis. Nevertheless, the magnitude of the association was in general estimated to be negligible to small (see Table 4A and 4B). Statistical significance and magnitude of the association varied and factors including gender, age, the severity of periodontitis, smoking status, and geographic location may affect the link between the periodontitis and CVD/CVE. However, it is important to note that there was considerable heterogeneity across the included clinical studies and directly comparing the SRs is challenging due to variations in the used approaches to assess periodontitis and CVD/ CVE among the included clinical studies. Besides the relatively negligible to small association between periodontitis and CVD/CVE the findings should also be interpreted with caution considering the limitations and potential biases in the data that emerged from the included studies.

The association between periodontitis and CVD

Previous papers have suggested a link between the two conditions due to their common causal components, such as lifestyle factors and smoking. 59-61 It is known that periodontitis causes chronic inflammation demonstrated with elevated plasma cytokines in gingiva and gingival fluid which inflammatory markers are also shown to be elevated systemically.62 The potential causal relationship between the two conditions could be explained by various mechanisms, including endothelial dysfunction, direct damage caused by periodontal pathogens, inflammation resulting from microbial byproducts, and immune reactions triggered by bacterial antigens. These factors collectively contribute to the development and progression of both conditions.⁶² This synthesis shows that the overall findings from multiple clinical studies suggest a significant association between periodontitis and various CVD outcomes. The overall available evidence suggests a statistically significant link between periodontitis and CVD, particularly for CHD and ACVD. However, when interpreting the RRs and ORs, the magnitude of the association of periodontitis and CVD was estimated to ranges from negligible to medium (Table 3A and Table 4). The heterogeneity among the studies should also be considered as this may has an impact on the interpretation of the findings. The variations in study design, measurement tools, and adjustment for confounding factors contribute to the heterogeneity observed. Moreover, some studies have suggested potential biases and confounding factors that could affect the accuracy of the findings.

The association between periodontitis and CVE

In accordance with a recent consensus report by Sanz et al., 63 which stated that patients with periodontitis have an elevated risk for both stroke and MI, this synthesis shows evidence of a higher risk of stroke in patients with periodontitis compared to those without. Sensitivity analyses and subgroup analyses were conducted in some studies, revealing that high-quality studies tended to show a stronger association between periodontitis and stroke, while low-quality studies showed weaker but still significant associations (XI48). These differences were also notable when interpreting the extracted ORs and RRs, showing that the magnitude of the

association could be interpreted to range from none to medium for most meta-analysis, yet large for meta-analysis outcomes of high-quality studies (Table 3A and Table 4).

A recent publication in the Journal of the American Dental Association⁶⁴ revealed an elevated risk of hospitalization due to MI in patients with periodontitis. While this synthesis similarly indicates a higher risk for MI, the findings lack consistent statistical significance. The meta-analyses showed conflicting results, with observed ORs ranging from 1.09 to 1.20 (XIV⁵¹ and XVIII⁵⁵, Table 3A) for MI in patients with periodontitis, suggesting a negligible to marginally magnitude of association. Varying quality among analyzed SRs, differences in study design, population characteristics, and data analysis contribute to heterogeneity in the studies. In summary, a consistent and significant association between periodontitis and an increased risk of stroke is observed, whereas the evidence for a link between periodontitis and MI is less conclusive. Nevertheless, for both CVE it is important to consider that mostly a small magnitude of the association between periodontitis and CVE emerged (Table 3A and 4B).

Individual factors contributing the association?

Several of the included SRs examined gender, age, periodontitis severity, smoking status and/or study region in relation to the potential association of periodontitis and CVD/CVE. Previous studies have indicated potential variations in systemic pathologies between males and females due to hormonal gender differences. ^{65,66} Still, the findings regarding to the influence of gender on the association between periodontitis and CVD/CVE are inconsistent. Some SRs suggest a stronger association in men (III⁴²), while others indicate a higher risk in women (VI, ⁴⁵ XII⁴⁹ and XIX, ⁵⁶ Table 3B). But the differences in risk between genders were generally not found to be statistically significant and influence of the magnitude of the association was estimated to range from none to small.

Based on the findings of three SRs (II,⁴¹ III⁴² and VII,³⁸ Table 3B) age was estimated to have an impact on the association between periodontitis and CVD/CVE. Younger individuals appear to have stronger associations with CHD, while there is no clear association in individuals of 65 years and above (III⁴² and VII,⁴¹ Table 3B). Additionally, the risk of CHD is further increased in individuals aged 65 years or younger with periodontitis. A similar observation is reported in a recently published critical appraisal,⁶⁷ emphasizing the age-dependent association between ACVD and periodontitis. Generally, in men older than 60 years no discernible association is identified between periodontitis and the incidence of CVE.⁶⁷

In accordance with the consensus report of Sanz et al., 63 this synthesis shows that the severity of periodontitis is consistently associated with a higher risk of CVD and CVE, showing an association between periodontitis and CVD/CVE with an estimated range of negligible to small (III, 42 X, 47 XVI 53 and XIX, 56 Table 3B). However, it should be noted that there was heterogeneity between the studies in periodontitis severity description and only four SRs specifically analyzed the magnitude of the association of periodontitis severity on the relationship between periodontitis and CVD/CVE. Therefore, the observed associations in this synthesis should be interpreted with caution.

The findings regarding the influence of smoking on the association between periodontitis and CVD/CVE are conflicting. One SR (III⁴²) found an association suggesting that the relationship between periodontitis and CVD/CVE may be stronger in non-smokers compared to those who have smoked before. Contrary, one other SR (XVI,⁵³ Table 3B) stated that there is an increased risk of CVD and CVE associated with periodontitis among smokers. However, it is important to note that these findings are based on limited evidence since both SRs mentioned that their findings relied on a single clinical study to support their conclusions regarding the association between smoking status, periodontitis, and CVD/CVE.^{68,69} Additionally, it is important to consider the broader context and acknowledge the existing literature that highlights the

relationship between smoking, periodontitis, and CVD/CVE. There is evidence that smoking causes a persistent inflammatory response, which affects fibrocyte function and tissue healing. This response is linked as a risk factor to both periodontitis and CVD/CVE.⁷⁰ Given these associations, smokers with periodontitis should be aware of the potential increased risk of CVD/CVE and take active measures to control their cardiovascular risk factors, including smoking cessation.⁶³

The emerging evidence for this synthesis suggests a negligible to medium influence of the geographic area of origin on the observed risk of CVD/CVE in patients with periodontitis (II⁴¹ and X,⁴⁷ Table 3B). Subgroup analyses showed higher ORs for CVD/CVE in people with periodontitis from Europe, South America, North America, and Scandinavian countries compared to other regions (II,⁴¹ Table 3B). Specifically, comparing European studies to Asia and Australia, higher incident risk of CVD/CVE was found for studies conducted in Europe (X⁴⁷) (Table 3B). But only one SR found these differences to be statistically significant (XII⁴⁹) (Table 3B).

Interpretation of the magnitude of the association

Tables 4A and 4B illustrate a concise summary and interpretation of the results obtained from Table 3A. In this context, an effort was made to synthesize the dispersion of values for both RRs and ORs, ultimately showing the overall most frequent reported magnitude of the association. Yet, it is important to critically assess the interpretative value of this approach and acknowledge that the interpretation of Table 4A and 4B may have limitations. While it offers a simplified overview of the dispersion and the overall most frequent reported magnitude of the association of RRs and ORs, it should be viewed as a preliminary step in synthesizing the data emerging form the included SRs.

As shown in Table 3A and 4A, the magnitude of the association between periodontitis and CVD was found to range from negligible to medium. This could be attributed to the presence of shared risk factors. It is known that both conditions share common causal components such as smoking, DM, and genetic predisposition. As a result, the observed association may be attenuated or diluted due to the overlapping influence of these shared risk factors. Therefore, it is important to consider these shared risk factors when evaluating the association between periodontitis and CVD to more accurately assess the potential impact of periodontitis on cardiovascular health. On the other hand, a noteworthy consideration is that the meta-analyses with outcomes that ranged for small to medium consist of relatively smaller sample sizes (Table 3A). This observation raises an important point regarding the impact of sample size estimation on the magnitude of the association in meta-analyses. In those studies that included smaller sample sizes, the precision of the outcomes tends to be lower.⁷³

The magnitude of the association that emerged from the meta-analysis with respect to the association of periodontitis and CVE ranged from negligible to large (Table 3A and 4B). The findings presented indicate that there is a notable difference in the interpretable magnitude of the association of the ORs and RRs especially for stroke across the different SRs (Table 3A). Specifically, the meta-analyses of high-quality studies and case-control studies conducted by SR XI⁴⁸ showed a large magnitude of the association, suggesting a strong association between periodontitis and stroke. However, it is worth noting that two years later, another SR was conducted (IV⁴³), which included also two of the primary clinical studies previously examined by SR XI⁴⁸ (Online Appendix S3). Despite these two case-control studies being considered high-quality studies by the reviewers of SR XI⁴⁸, the magnitude of the association calculated in the meta-analysis in SR IV⁴³ decreased to a medium level after the inclusion of more recent clinical studies (Table 3A). This observation suggests that the genuine magnitude of the association between the variables is likely to be lower than initially estimated by SR XI.⁴⁸ The inclusion of newer studies, which may have contributed additional data and insights, led to a reduction

in the magnitude of the association. This emphasizes the importance of considering the cumulative evidence and the potential impact of new studies on values emerging from the meta-analyses. Furthermore, it is worth noting that there is notable overlap among the primary clinical studies included in the SRs, with RRs and ORs indicating values ranging from small to large magnitude (Online Appendix S2). Additionally, except for SR X,⁴⁷ the meta-analyses with an estimated small to large association consist of relatively smaller sample sizes (Table 4B).⁷³ Furthermore, SR IV⁴³ primarily analyze the association through cohort and case-control studies. Therefore, the reliability of these results is called into question by the review authors due to substantial heterogeneity among the included SRs. It is essential to recognize and acknowledge this heterogeneity, underscoring the importance of approaching the interpretation with caution and considering potential limitations, particularly the impact of variations between the included studies.

Citation matrix

When examining multiple SRs, it is important to review the primary studies and compare them to identify any potential overlap. ^{27,74} For this synthesis a citation matrix was prepared to create a comprehensive overview of primary clinical studies as included in the underlying SRs. ²⁷ This helps to ensure that the conclusions drawn are based on a diverse range of studies. The primary studies mostly included in multiple SRs are Destefano et al., ⁷⁵ Beck et al., ⁵⁹ Joshipure et al., ⁷⁶ Wu et al., ⁷⁷ Morrisson et al. ⁷⁸ and Howell et al., ⁷⁹ with publication dates between 1993 and 2001 (Online Appendix S3).

With an overlap of seven to 10 primary study inclusions in SRs, it may be suggested that these studies provide valuable and reliable evidence in investigating the possible link between periodontitis and CVD/CVE (Online Appendix S3). Those studies included a substantial number of participants and were of considerable epidemiological scale. Additionally, the authors found similar outcomes showing an increased risk of CVD/CVE for patients with periodontitis which strengthens the confidence in the findings and increases the robustness of the evidence. Consistency across multiple reviews adds weight to the results and enhances the reliability of the conclusions drawn from the collective body of evidence.¹⁸

Conversely, the overlap in primary studies has the potential to artificially inflate the accuracy of the analysis by overestimating the sample size and events. Including the same study multiple times in an analysis could influence the results and unwarranted weight. Overlapping reviews could also be indicating excessive research efforts. To ensure precision and reliability in SRs, addressing the overlap issue is imperative. Nevertheless, a standardized methodological approach to manage the inclusion of clinical studies across multiple SRs lacks consensus.

Appraisal of the evidence

The present synthesis is a comprehensive evaluation of existing SRs, aiming to include all available reviews and conducting a thorough assessment of each included review.⁸¹ The rigorous methodology, incorporating established checklists such as PRISMA,^{20,21} AMSTAR²² and the JBI¹⁹ guidelines facilitated the assessment of the quality and validity of the included SRs. The PRISMA checklist²⁰ guided the systematic review process, promoting transparency and completeness in reporting the search strategy, study selection, and data extraction. The utilization of the AMSTAR checklist²² allowed for a comprehensive assessment of the methodological quality of the included SRs, encompassing aspects such as study design, bias evaluation, and statistical analysis. Additionally, the JBI checklist¹⁹ played a central position in critically appraising the quality of evidence and further strengthening the review's reliability. Through strict adherence to these standardized checklists, this synthesis minimized potential

biases, enhancing the credibility and robustness of the synthesized evidence.

The results of the PRISMA^{20,21} and AMSTAR²² modified checklists are displayed in Table 2 and Online Appendix S2+S8, indicate that the assessed risk of bias is predominantly categorized as low to moderate. Two SRs (VII³⁸ and VIII³⁹) included in this review were identified to have a substantial risk of bias based on critical evaluation criteria. Notably, these reviews had earlier publication dates than the other SRs included, suggesting that there may have been variations in the requirements and standards for conducting SRs at that time. Additionally, this observation implies that over time, there is a trend towards conducting more robust and higher-quality qualitative SRs in this field.

In evaluating the association between periodontitis and CVD/CVE, this synthesis applies both the Bradford Hill criteria¹⁸ and the GRADE³⁴ approach, revealing an overlap between the two frameworks (Table 5 and 6). A previous publication highlights this finding, indicating the ongoing influence of the Bradford Hill criteria¹⁸ and the use of other approaches, such as GRADE³⁴ for understanding the viewpoints of Bradford Hill¹⁸. By integrating GRADE³⁴ principles, it becomes evident why the criterion of specificity may have limited applicability in causal inference. When it comes to causal assessment the need for an enhanced clarity and standardization in the field of epidemiology has previous been noted.82 The Bradford Hill criteria18 continue to hold a fundamental importance in causal assessment and SRs and epidemiological studies consistently demonstrate an association between periodontitis and CVD/CVE.82 This synthesis assessed the causality of the relationship between periodontitis and CVD/CVE by applying the Bradford Hill criteria. 18 The consistent findings across SRs, the presence of a biological gradient, and the plausibility of shared mechanisms all may suggest a potential causal link. However, the magnitude of the association could be considered mostly negligible to small. Additionally, other criteria such as specificity, temporality, experimental evidence and analogy were not fully explored in this synthesis, limiting the assessment of causality. It is important to acknowledge that the present findings do not provide definitive evidence for establishing causality. The findings from the assessment of Bradford Hill criteria support the analysis in a recent narrative review that critically appraised the association between periodontitis and ACVD.⁶⁷ The authors of this review concluded that, based on Bradford Hill's criteria, ¹⁸ no definitive conclusion can be drawn regarding the causal relationship between periodontitis and ACVD.⁶⁷ As of now, there is a lack of evidence addressing the crucial issue of the temporal relationship between exposures and outcomes.

It remains to be determined whether future investigations will yield a positive estimate for meeting Bradford Hill criteria. Establishing causality through intervention studies remains challenging. The lack of well-designed, blinded randomized controlled trials with CVD/CVE outcomes is a significant limitation. Conducting high quality, double blinded, randomized controlled trials with periodontitis and CVD/CVE outcomes is on the other hand complicated due to ethical considerations.

Furthermore, the discussion surrounding the association between periodontitis and CVD/CVE raises intriguing points. According to SR VI,45 the absence of a clear causal relationship between periodontitis and CHD suggests the possibility of periodontitis serving as a risk marker rather than a direct cause. This perspective introduces the concept of unexplained confounding, where a factor connected to both periodontitis and CHD, such as smoking, diet, DM, or socio-economic status, may contribute to the observed association. SR VIII³⁹ reaffirms this viewpoint, suggesting that reported positive associations could be influenced by biases or residual confounding, given shared risk factors like age, smoking, stress, socio-economic status, body fat content, and health consciousness. Consequently, the review authors of SR VIII³⁹ express uncertainty about whether the association between periodontitis and CVD/CVE is specific or coincidental. Furthermore, SR XVI⁵³ acknowledges an association

between periodontitis and CVD/CVE but emphasizes that the causal mechanism underlying this link is not yet well-established. These discussions collectively underscore the complexity of the relationship between periodontitis and CVD/CVE, urging further research to clarify the intricacies and nature of their association.

Limitations

- In this synthesis, the decision to exclusively include individuals aged ≥16 years, excluding those <16 years, was made due to the acknowledged significant role of genetics in the development of both periodontitis and CVD/CVE, particularly at a younger age.⁷² This focus aimed to mitigate the potential confounding effects of genetic factors on the observed association between periodontitis and CVD/CVE parameters.
- In this synthesis, CVD/CVE were defined as CVD or CVE, with a focus on specific and clinically relevant evidence for the potential association. However, excluding parameters like hypertension, atrial fibrillation, arterial stiffness, arterial calcification, and surrogate markers for CVD/ CVE outcomes may limit the comprehensive understanding of the relationship between periodontitis and CVD/CVE. While these parameters are established risk factors for CVD/CVE, their exclusion could overlook important subclinical manifestations or early indicators of cardiovascular damage relevant to periodontitis. 11,83-89 Conversely, by excluding these intermediate parameters and relying on actual CVD/CVE, the synthesis ensures a more robust assessment of the direct impact, providing specific and clinically relevant evidence on the association between periodontitis and CVD/CVE.
- It is also important to recognize that both periodontitis and CVD/CVE are multifactorial conditions, with their development involving a complex interplay of various causal components. 14,90
- As this synthesis of SRs analyzed pooled ORs and RRs from included SRs, direct comparisons of meta-analysis outcomes between studies may yield inconsistent interpretations of association strength. The interchangeability of fixed and random effects models in these studies poses a challenge for direct comparisons, as these models make different assumptions about underlying variability. Therefore, when assessing SRs using different models and outcome parameters, the potential impact of these methodological differences on the findings should be considered.
- A limitation of the synthesis of SRs lies in the use of meta-analysis for observational studies. While meta-analysis proves valuable for comprehending variability across studies, it introduces challenges due to inherent biases and divergent study designs. The potential for publication bias further complicates the synthesis, emphasizing the need for cautious interpretation and consideration of these limitations in drawing conclusions from the merged findings.
- It is also important to recognize that both periodontitis and CVD/CVE are multifactorial conditions, with their development involving a complex interplay of various causal components. He is a metabolic disease, adversely affects periodontal and cardiovascular health through microvascular changes and endothelial dysfunction. Complications impact bone health and contribute significantly to periodontitis. DM is a confirmed risk factor for periodontitis and CVD/CVE. Laceton Excluding DM patients in this synthesis clarifies the direct association but limits broader applicability. By omitting this population, the review may fall short of fully capturing the potential impact of periodontal disease on cardiovascular health in real-world settings, where patients having DM and metabolic syndrome are common.

Directions for future research

For future investigations into the association between periodontitis and CVD/CVE, there is a need for standardized definitions of both conditions and meticulous adjustment for confounding factors. This approach is essential to gain a more comprehensive understanding of their relationship. Moreover, beyond these considerations, a priority should be placed on exploring the biological mechanisms. This emphasis aims to enhance our understanding of the potential causal relationship between periodontitis and CVD/CVE.

CONCLUSION

This synthesis of SRs provides insights into the association between periodontitis and CVD/CVE. With moderate certainty, the magnitude of this association can generally be estimated as negligible to small, and causality, according to Bradford Hill criteria, remains undefined. It is noteworthy that factors such as gender, age, periodontitis severity, smoking status, and geographic region may be confounders on the association between periodontitis and CVD/CVE. This nuanced understanding underscores the complexity of the relationship and emphasizes the need for ongoing exploration in future research.

CLINICAL RELEVANCE

Scientific rationale for this analysis

Given the high prevalence of period and CVD/CVE and their shared risk factors, there is a growing interest in understanding the association between these conditions.

Principle findings

Regarding the relationship between periodontitis and CVD/CVE, there is moderate certainty indicating a negligible to small association. Therefore, the link between periodontitis and CVD/CVE remains inconclusive, and causality in their relationship has not yet been definitively identified.

Practical implications

In absence of a potential association, it remains important to maintaining good oral health for overall well-being, as periodontitis can also negatively affect quality of life.

Online Appendices



STATEMENTS

Acknowledgements

The authors acknowledge the support of Joost Bouwman, head librarian of the Academic Centre for Dentistry Amsterdam, who helped in the retrieval of the full-text articles.

Statement of ethics

This research has been approved by the ACTA Institutional review board, by reference number 2022-74229 and registered at the International Prospective Register of Systematic Reviews (PROSPERO) by number CRD42023444999.

Conflict of interest statement

The first author and co-authors declare that they have no conflicts of interest.

Funding sources

This paper was prepared as part of the obligation of the first author to fulfil the requirements of the ACTA Master's program in dentistry. This review was self-funded by the authors and their institution.

Data statement

All data generated or analyzed during this study are included in this article and the onlince appendices. Further enquiries can be directed to the corresponding author.

Author contributions

MGPS: contributed to design, search and selection, analysis and interpretation, and drafted the manuscript.

LPMW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

EJSW: contributed to search and selection and critically revised the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

REFERENCES

The papers included in this synthesis are highlighted in **bold** in the list.

- 1. Chapple ILC, Van Der Weijden F, Doerfer C, et al. Primary prevention of periodontitis: Managing gingivitis. *J Clin Periodontol*. 2015;42(S16):S71-S76. doi:10.1111/JCPE.12366
- 2. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol*. 2018;89:S173-S182. doi:10.1002/JPER.17-0721
- 3. van der Velden U. 5 Classificatie van parodontitis. In: Beertsen W, Quirynen M, van Steenberghe D, van der Velden U, eds. *Parodontologie*. Bohn Stafleu van Loghum; 2009;51-53. doi:10.1007/978-90-313-6887-7 5
- 4. Sanz M, D'aiuto F, Deanfield J, Fernandez-Avilés F. European workshop in periodontal health and cardiovascular disease-scientific evidence on the association between periodontal and cardiovascular diseases: a review of the literature. European Heart Journal Supplements. Published online 2010:3-12. doi:10.1093/eurheartj/suq003
- Kassebaum NJ, Smith AGC, Bernabé E, et al. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990-2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. J Dent Res. 2017;96(4):380-387. doi:10.1177/0022034517693566/ASSET/IMAGES/LARGE/10.1177 0022034517693566-FIG3.JPEG
- Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global burden of severe periodontitis in 1990-2010: A systematic review and meta-regression. *J Dent Res.* 2014;93(11):1045-1053. doi:10.1177/0022034514552491/ASSET/IMAGES/LARGE/10.1177 0022034514552491-FIG4.JPEG
- 7. De Wet LM, Slot DE, Van der Weijden GA. Supportive periodontal treatment: Pocket depth changes and tooth loss. *Int J Dent Hyg.* 2018;16(2):210-218. doi:10.1111/IDH.12290
- 8. Loos BG, Craandijk J, Hoek FJ, Dillen PMEW van, Velden U Van Der. Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients. *J Periodontol.* 2000;71(10):1528-1534. doi:10.1902/JOP.2000.71.10.1528
- 9. Linden GJ, Linden K, Yarnell J, Evans A, Kee F, Patterson CC. All-cause mortality and periodontitis in 60-70-year-old men: A prospective cohort study. *J Clin Periodontol*. 2012;39(10):940-946. doi:10.1111/j.1600-051X.2012.01923.x
- 10. Sharma P, Dietrich T, Ferro CJ, Cockwell P, Chapple ILC. Association between periodontitis and mortality in stages 3-5 chronic kidney disease: NHANES III and linked mortality study. *J Clin Periodontol*. 2016;43(2):104-113. doi:10.1111/jcpe.12502
- 11. Cardiovascular diseases (CVDs). Accessed December 23, 2023. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
- 12. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053):1459–1544. doi:10.1016/S0140–6736(16)31012-1
- 13. World Health Organization. The top 10 causes of death. December 2020. Accessed December 23, 2023. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
- 14. Zardawi F, Gul S, Abdulkareem A, Sha A, Yates J. Association Between Periodontal Disease and Atherosclerotic Cardiovascular Diseases: Revisited. *Front Cardiovasc Med.* 2021;7:401. doi:10.3389/FCVM.2020.625579/BIBTEX
- 15. Tonetti MS, Van Dyke TE. Periodontitis and atherosclerotic cardiovascular disease: Consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Clin Periodontol*. 2013;40(SUPPL. 14):24-29. doi:10.1111/jcpe.12089
- 16. Nabila S, Choi J, Kim JE, et al. Bidirectional associations between periodontal disease and systemic diseases: a nationwide population-based study in Korea. *Sci Rep.* 2023;13(1):14078. doi:10.1038/s41598-023-41009-4
- 17. Lavigne SE, Forrest JL. An umbrella review of systematic reviews of the evidence of a causal relationship between periodontal disease and cardiovascular diseases: Position paper from the Canadian Dental Hygienists Association. Canadian journal of dental hygiene. 2020;54(I):32-41. https://www.dentalcare.com/en-us/
- 18. Hill AB. The Environment and Disease: Association or Causation? In: *Proceedings of the Royal Society of Medicine*.; 1965:295-300.
- 19. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: Methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc*. 2015;13(3):132-140. doi:10.1097/XEB.000000000000055
- 20. PRISMA statement. Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Accessed December 23, 2023. http://www.prismastatement.org/
- 21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1). doi:10.1186/s13643-021-01626-4
- 22. AMSTAR. A measurement tool to assess systematic reviews. . Accessed December 23, 2023. http://amstar.ca/index.php
- 23. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good

- questions to explore the association of environmental and other exposures with health outcomes. *Environ Int.* 2018;121:1027-1031. doi:10.1016/J.ENVINT.2018.07.015
- 24. Ryan R, Cochrane Consumers, Communication Review Group. Cochrane Consumers and Communication Review Group: data synthesis and analysis. 2013. Accessed December 23, 2023. http://cccrg.cochrane.org
- 25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* 2016;5(1). doi:10.1186/s13643-016-0384-4
- 26. Nguyen M, Cohen J. Peripheral Vascular Disease. *Pain Medicine: An Essential Review*. Published online February 6, 2023;495-496. doi:10.1007/978-3-319-43133-8 131
- 27. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: practical considerations for authors of overviews of reviews. *BMC Med Res Methodol*. 2021;21(1):1–14. doi:10.1186/S12874-021-01269-Y/FIGURES/4
- 28. Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. http://dx.doi.org/101080/0361092620151134575. 2017;46(14):6774-6781. doi:10.1080/03610926.2015.1134575
- 29. Chen H, Cohen P, Chen S. How big is a big odds ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. Commun Stat Simul Comput. 2010;39(4):860-864. doi:10.1080/03610911003650383
- 30. Heterogeneity and subgroup analyses in Cochrane Consumers and Communication Group reviews: Planning the analysis at protocol stage, 2016. Accessed December 23, 2023. http://cccrg.cochrane.org,
- 31. Hidding JT, Beurskens CHG, Van Der Wees PJ, Van Laarhoven HWM, Nijhuis-van Der Sanden MWG. Treatment related impairments in arm and shoulder in patients with breast cancer: A systematic review. *PLoS One*. 2014;9(5). doi:10.1371/journal.pone.0096748
- 32. Sälzer S, Slot DE, Van Der Weijden FA, Dörfer CE. Efficacy of inter-dental mechanical plaque control in managing gingivitis A meta-review. *J Clin Periodontol*. 2015;42(S16):S92-S105. doi:10.1111/jcpe.12363
- 33. Van Der Weijden FA, Slot DE. Efficacy of homecare regimens for mechanical plaque removal in managing gingivitis a meta review. *J Clin Periodontol*. 2015;42(S16):S77-S91. doi:10.1111/jcpe.12359
- 34. GRADE home. Accessed December 23, 2023. https://www.gradeworkinggroup.org/
- 35. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/BMJ.39489.470347.AD
- 36. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines. *J Clin Epidemiol*. 2011;64(4):380-382. doi:10.1016/j.jclinepi.2010.09.011
- 37. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. *Biometrics*. 1977;33(1):159-174. https://about.istor.org/terms
- Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95(5):559-569. doi:10.1067/ moe.2003.107
- 39. Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. *J Periodontol*. 2004;75(8):1046-1053. doi:10.1902/jop.2004.75.8.1046
- 40. Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *Am Heart J.* 2007;154(5):830-837. doi:10.1016/j. ahj.2007.06.037
- 41. Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. *Int Dent J.* 2009;59(4):197-209. https://pubmed.ncbi.nlm.nih.gov/19774803/
- 42. Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. *J Clin Periodontol*. 2013;40:S70-84. doi:10.1111/jcpe.12062
- 43. Fagundes NCF, APCPSC A, Vilhena KFB, Magno MB, Maia LC, Lima RR. Periodontitis As A Risk Factor For Stroke: A Systematic Review And Meta-Analysis. *Vasc Health Risk Manag*. 2019;15:519-532. doi:10.2147/VHRM. S204097
- 44. Gao S, Tian J, Li Y, et al. Periodontitis and Number of Teeth in the Risk of Coronary Heart Disease: An Updated Meta-Analysis. *Med Sci Monit*. 2021;27:e930112. doi:10.12659/MSM.930112
- 45. Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. *J Gen Intern Med.* 2008;23(12):2079-2086. doi:10.1007/s11606-008-0787-6
- 46. Lafon A, Pereira B, Dufour T, et al. Periodontal disease and stroke: a meta-analysis of cohort studies. *Eur J Neurol*. 2014;21(9):1155-1161, e66-7. doi:10.1111/ene.12415
- 47. Larvin H, Kang J, Aggarwal VR, Pavitt S, Wu J. Risk of incident cardiovascular disease in people with periodontal disease: A systematic review and meta-analysis. *Clin Exp Dent Res.* 2021;7(1):109-122. doi:10.1002/cre2.336
- 48. Leira Y, Seoane J, Blanco M, et al. Association between periodontitis and ischemic stroke: a systematic review and meta-analysis. *Eur J Epidemiol*. 2017;32(1):43-53. doi:10.1007/s10654-016-0170-6
- 49. Meregildo-Rodriguez ED, Robles-Arce LG, Chunga-Chévez EV, Asmat-Rubio MG, Zavaleta-Alaya P, Vásquez-Tirado GA. Periodontal disease as a non-traditional risk factor for acute coronary syndrome: a systematic review and meta-analysis. *Infezioni in Medicina*. 2022;30(4):501-515. doi:10.53854/liim-3004-4

- 50. Orlandi M, Suvan J, Petrie A, et al. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: a systematic review and meta-analysis. *Atherosclerosis*. 2014;236(1):39-46. doi:10.1016/j.atherosclerosis.2014.06.002
- 51. Qin X, Zhao Y, Guo Y. Periodontal disease and myocardial infarction risk: A meta-analysis of cohort studies. *Am J Emerg Med.* 2021;48:103-109. doi:10.1016/j.ajem.2021.03.071
- 52. Sfyroeras GS, Roussas N, Saleptsis VG, Argyriou C, Giannoukas AD. Association between periodontal disease and stroke. *J Vasc Surg.* 2012;55(4):1178-1184. doi:10.1016/j.jvs.2011.10.008
- 53. Voinescu I, Petre A, Burlibasa M, Oancea L. Evidence of Connections Between Periodontitis and Ischemic Cardiac Disease an Updated Systematic Review. *Maedica (Bucur)*. 2019;14(4):384-390. doi:10.26574/maedica.2019.14.4.384
- 54. Wang J, Geng X, Sun J, et al. The risk of periodontitis for peripheral vascular disease: a systematic review. *Rev Cardiovasc Med*. 2019;20(2):81-89. doi:10.31083/j.rcm.2019.02.52
- 55. Xu S, Song M, Xiong Y, Liu X, He Y, Qin Z. The association between periodontal disease and the risk of myocardial infarction: a pooled analysis of observational studies. *BMC Cardiovasc Disord*. 2017;17(1):50. doi:10.1186/s12872-017-0480-y
- 56. Zeng XT, Leng WD, Lam YY, et al. Periodontal disease and carotid atherosclerosis: A meta-analysis of 17,330 participants. *Int J Cardiol*. 2016;203:1044-1051. doi:10.1016/j.ijcard.2015.11.092
- 57. Wang J, Yang X, Zou X, Zhang Y, Wang J, Wang Y. Relationship between periodontal disease and lung cancer: A systematic review and meta-analysis. *J Periodontal Res.* 2020;55(5):581-593. doi:10.1111/jre.12772
- 58. Lavigne S. From Evidence to Causality: How Do We Determine Causality? [Online course]. 2018. Accessed December 23, 2023. www.dentalcare.com/en-us/professional-education/ce-courses/ce530
- 59. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal Disease and Cardiovascular Disease. *J Periodontol*. 1996;67(10s):1123-1137. doi:10.1902/JOP.1996.67.10S.1123
- 60. Loesche WJ, Schork A, Terpenning MS, Chen YM, Dominguez L, Grossman N. Assessing the Relationship between Dental Disease and Coronary Heart Disease in Elderly U.S. Veterans. *Journal of the American Dental Association*. 1998;129(3):301-311. doi:10.14219/jada.archive.1998.0204
- 61. Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. Relationship of Periodontal Disease to Carotid Artery Intima-Media Wall Thickness. *Arterioscler Thromb Vasc Biol.* 2001;21(11):1816-1822. doi:10.1161/HQ1101.097803
- 62. Choi H, Dey AK, Priyamvara A, et al. Role of Periodontal Infection, Inflammation and Immunity in Atherosclerosis. *Curr Probl Cardiol*. 2021;46(3):100638. doi:10.1016/j.cpcardiol.2020.100638
- 63. Sanz M, Marco del Castillo A, Jepsen S, et al. Periodontitis and cardiovascular diseases: Consensus report. *J Clin Periodontol.* 2020;47(3):268-288. doi:10.1111/JCPE.13189
- 64. Nalliah RP, Basu T, Chang CH. Association between periodontal care and hospitalization with acute myocardial infarction. *Journal of the American Dental Association*. 2022;153(8):776-786.e2. doi:10.1016/j.adaj.2022.02.003
- 65. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. *Int J Health Sci* (*Qassim*). 2017;11(2):72. Accessed December 23, 2023, /pmc/articles/PMC5426403/
- 66. Marchetti E, Monaco A, Procaccini L, et al. Periodontal disease: the influence of metabolic syndrome. *Nutr Metab* (Lond), 2012;9:88, doi:10.1186/1743-7075-9-88
- 67. Carra MC, Rangé H, Caligiuri G, Bouchard P. Periodontitis and atherosolerotic cardiovascular disease: A critical appraisal. *Periodontol* 2000. Published online 2023, doi:10.1111/PRD.12528
- Dorn JM, Genco RJ, Grossi SG, et al. Periodontal disease and recurrent cardiovascular events in survivors of myocardial infarction (MI): the Western New York Acute MI Study. J Periodontol. 2010;81(4):502-511. doi:10.1902/ JOP.2009.090499
- 69. Carallo C, Irace C, Tripolino C, et al. Time course analysis of brachial artery flow mediated dilatation in subjects with gingival inflammation. *Int Angiol.* 2014;33(6):565-572.
- 70. Gomes-Filho IS, Coelho JMF, Miranda SS, et al. Severe and moderate periodontitis are associated with acute myocardial infarction. *J Periodontol*. 2020;91(11):1444-1452. doi:10.1002/JPER.19-0703
- 71. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of Periodontal Pathogens in Atheromatous Plaques. *J Periodontol*. 2000;71(10):1554-1560. doi:10.1902/JOP.2000.71.10.1554
- 72. Hodge P, Michalowicz B. Genetic predisposition to periodontitis in children and young adults. *Periodontol 2000*. 2001;26(1):113-134. doi:10.1034/J.1600-0757.2001.2260106.X
- 73. Faber J, Fonseca LM. How sample size influences research outcomes. *Dental Press J Orthod*. 2014;19(4):27. doi:10.1590/2176-9451.19.4.027-029.EBO
- 74. Hennessy EA, Johnson BT. Examining Overlap of Included Studies in Meta-Reviews: Guidance for using the Corrected Covered Area Index. Res Synth Methods. 2020;11(1):134-145. doi:10.1002/jrsm.1390
- 75. Destefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. *Br Med J.* 1993;306:688-691. doi:10.1136/bmj.306.6879.688
- 76. Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor Oral Health and Coronary Heart Disease. *J Dent Res.* 1996;75(9):1631-1636. doi:10.1177/00220345960750090301
- 77. Wu T, Trevisan M, Genco RJ, Dorn JP, Falkner KL, Sempos CT. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. *Arch Intern Med.*

- 2000;160(18):2749-2755. doi:10.1001/ARCHINTE.160.18.2749
- 78. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk*. 1999;6(1):7-11. Accessed December 23, 2023. https://academic.oup.com/eurjpc/article/6/1/7/5927555
- 79. Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. *J Am Coll Cardiol*. 2001;37(2):445-450. doi:10.1016/S0735-1097(00)01130-X
- 80. Pérez-Bracchiglione J, Meza N, Bangdiwala SI, et al. Graphical Representation of Overlap for OVErviews: GROOVE tool. Res Synth Methods. 2022;13(3):381-388. doi:10.1002/JRSM.1557
- 81. Sarrami-Foroushani P, Travaglia J, Debono D, Braithwaite J. Key concepts in consumer and community engagement: A scoping meta-review. *BMC Health Serv Res.* 2014;14(1):1-9. doi:10.1186/1472-6963-14-250/TABLES/1
- 82. Febbraio M, Roy CB, Levin L. Concise Clinical Review Is There a Causal Link Between Periodontitis and Cardiovascular Disease? A Concise Review of Recent Findings. *Int Dent J.* 2022;72:37–51. doi:10.1016/j.identj.2021.07.006
- 83. Figuero E, Sánchez-Beltrán M, Cuesta-Frechoso S, et al. Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. *J Periodontol*. 2011;82(10):1469-1477. doi:10.1902/JOP.2011.100719
- 84. Spahr A, Klein E, Khuseyinova N, et al. Periodontal infections and coronary heart disease: role of periodontal bacteria and importance of total pathogen burden in the Coronary Event and Periodontal Disease (CORODONT) study. *Arch Intern Med.* 2006;166(5):554–559. doi:10.1001/ARCHINTE.166.5.554
- 85. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J.* 2006;27(21):2588-2605. doi:10.1093/EURHEARTJ/EHL254
- 86. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98(10):946–952. doi:10.1161/01.CIR.98.10.946
- 87. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-988. doi:10.1161/01.STR.22.8.983
- 88. Fani L, Van Der Willik KD, Bos D, et al. The association of innate and adaptive immunity, subclinical atherosclerosis, and cardiovascular disease in the Rotterdam Study: A prospective cohort study. *PLoS Med.* 2020;17(5):e1003115. doi:10.1371/JOURNAL.PMED.1003115
- 89. Cardiovascular diseases PAHO/WHO | Pan American Health Organization. Accessed December 23, 2023. https://www.paho.org/en/topics/cardiovascular-diseases
- 90. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *The Lancet*. 2005;366(9499):1809-1820. doi:10.1016/S0140-6736(05)67728-8
- 91. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. *J Diabetes Complications*. 2006;20(1):59-68. doi:10.1016/J.JDIACOMP.2005.05.006
- 92. Apoorva SM, Sridhar N, Suchetha A. Prevalence and severity of periodontal disease in type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus) patients in Bangalore city: An epidemiological study. *J Indian Soc Periodontol*. 2013;17(1):25. doi:10.4103/0972-124X.107470
- 93. Gomes-Filho IS, Balinha I da SCE, da Cruz SS, et al. Moderate and severe periodontitis are positively associated with metabolic syndrome. *Clin Oral Investig.* 2021;25(6):3719-3727. doi:10.1007/S00784-020-03699-2/TABLES/3
- 94. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training. Accessed December 23, 2023. https://training.cochrane.org/handbook
- 95. Hunter JE, Schmidt FL. Fixed Effects vs. Random Effects Meta-Analysis Models: Implications for Cumulative Research Knowledge. *International Journal of Selection and Assessment*. 2000;8(4):275-292. doi:10.1111/1468-2389.00156

"t löp wa los"

Lotte Weijdijk

CHAPTER THREE

The association of periodontitis with diabetes mellitus

A synthesis of systematic reviews

E.J.S. Willems*, **L.P.M. Weijdijk***, M.G.P. Schoenmakers, G.A. Van der Weijden, D.E. Slot *International Journal of Dental Hygiene (submitted)*

*L.P.M. Weijdijk and E.J.S. Willems equally contributed to this paper.



ABSTRACT

Focused question

What is the association of periodontal disease and diabetes mellitus (DM) as reported in systematic reviews (SRs)?

Methods

MEDLINE-PubMed and Cochrane-CENTRAL databases were searched up to September 2024 for SRs that primarily evaluated the presence or absence of DM in periodontitis patients compared to non-periodontitis individuals. Data and conclusions as presented in the selected papers were extracted and the potential risk of bias was estimated using the PRISMA (2020) guideline and the AMSTAR (2017) checklists. A citation analysis was performed, and the Bradford Hill criteria were assessed. The body of evidence and the strength of recommendations was graded using GRADE.

Results

After screening of 487 titles and abstracts and full-text reading of potentially relevant paper, four SRs with seven meta-analyses were included. The majority (57%) of the reported risk ratios and odds ratios estimated a small magnitude of the association of periodontitis and DM. For 29% the association was considered to be negligible. Sub-analyses showed that factors such as gender, severity of periodontitis, smoking status, and geographical location were associated with the observed relationship. After applying the Bradford Hill criteria, a definitive confirmation of causality could not be established, as only three of the nine criteria were met. With moderate certainty, a negligible to small association of periodontitis and DM was identified.

Conclusion

A negligible to small association was found between periodontitis and DM. However, causality could not be confirmed.

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic and chronic disorder that stems from the body's inability to efficiently utilize the produced insulin or from insufficient insulin production. Insulin plays a vital role in maintaining metabolic balance for regulating blood glucose levels.¹ The World Health Organization (WHO) diagnosed DM within fasting plasma glucose (FPG) \geq 126 mg/dL (\geq 7.0 mmol/L) or glycated haemoglobin (HbA1c) \geq 6.5% (48 mmol/mol).².³ DM is a common and serious health problem.²-⁴ In recent decades, there has been a continuous increase in both the number of DM cases and its prevalence. In 2019, the global prevalence of DM I and II was estimated at 9.3%, projected to increase to 10.2% (578 million) in 2030 and 10.9% (700 million) in 2045.⁵

Periodontitis is a chronic inflammatory disease characterized by the progressive loss of tooth support from the periodontium, including the periodontal ligament and alveolar bone. Estimates suggest that it affects a significant proportion of the global population, with a prevalence rate of 20-50% of all individuals worldwide, with severe forms of the disease affecting approximately 11% of the global population. ⁶⁻⁸ Periodontitis has received increasing global attention due to its adverse effects on systemic health, particularly on DM. ⁹⁻¹² It is considered the sixth complication of DM. ^{8,13-15}

Periodontitis and DM have some shared risk factors such as age, smoking habits and obesity. Given the high prevalence of periodontitis and DM, as well as their shared risk factors, there is a growing interest in understanding the association between these two conditions. Most studies have focused on investigating the effect of DM on periodontitis parameters. DM patients have an increased risk of onset periodontitis and a greater severity of periodontal disease. Currently, inadequately controlled DM (HbA1C \geq 7%) is recognized as a risk factor for periodontitis as the gingival reaction to bacterial plaque among individuals with DM is influenced by the level of glycaemic control.

Recent scientific evidence has also evaluated the relationship of periodontitis on DM values. However, the majority of studies have focused on investigating the effect after non-surgical periodontal therapy (NSPT). A recent umbrella review indicated that NSPT is an efficacious therapy for improving glycaemic control in DM type II patients 3 to 6 months post-therapy. Moreover, NSPT is associated with HbAlc reductions of approximately 0.4%.^{23,24} Recently, an umbrella review examined the possible causal relationship of periodontitis to DM type Il determining if periodontal therapy lowers the risk of DM.25 lt was found that there was insufficient evidence to propose that NSPT improves individual HbAic values, so the exact nature of the relationship still remains unclear.²⁵ Despite the growing body of literature on the relationship between periodontitis and DM, there is limited evidence that only focused on the association between periodontitis (rather than NSPT) and the parameters of DM. Moreover, many review papers claim an association²⁶⁻²⁸ but no strong evidence supports a clear causal relationship. Given all this there appears to be a need for a comprehensive and critical appraisal of the available evidence concerning the association between periodontitis and DM and in addition estimate the potential causal link between these two conditions. Therefore, the aim of this study was to undertake a synopsis of synthesis (meta-review, MR) to consolidate and present the up-to-date evidence regarding the association of periodontitis with DM.

METHODS

A protocol was developed 'a priori' following initial discussion between the members of the research team. This MR was conducted and presented following the methodological guideline provided by the Joanna Briggs Institute (JBI)^{29,30}, as well as adhering to the PRISMA guideline^{31,32}, utilizing the AMSTAR tool³³, and the guideline for Meta-Analysis of Observational Studies in Epidemiology (MOOSE)³⁴ to ensure the methodological quality of the review process and improve the strength of reporting.

This MR is registered at the International Prospective Register of Systematic Reviews (PROSPERO) by number CRD42024512767. The Academic Centre for Dentistry Amsterdam (ACTA) Institutional Review Board has also provided approval with the following number: 2022-48457.

Focused question

A precise review question was formulated utilising the population, exposure, comparison, outcomes and study (PECOS)³⁵ framework as follows:

What association can be identified in individuals (P) with periodontitis (E) as opposed to those without periodontitis (C) with DM (O), based on information gathered from existing systematic reviews (SRs) with a meta-analysis (S)?

Search strategy

For the comprehensive search strategy, electronic databases including the National Library of Medicine, Washington, DC (MEDLINE-PubMed) and special collections of Cochrane-CENTRAL were used to search for applicable SRs. The databases were systematically queried up to September 2024. Two reviewers (EJSW and DES) collaboratively designed the search, with the aim of comprehensively reviewing all SRs that addressed the specific research question. Detailed information regarding the search terms can be found in Table 1. Additionally, the references cited in the included studies were examined to identify any supplementary relevant SRs. The PROSPERO database was consulted to ascertain the existence of ongoing reviews. No additional unpublished work or grey literature was sought.

Table 1

Search strategy used for MEDLINE-PubMed.

{[<exposure>] AND [<outcome>]}

<Exposure>

 $<\!((\text{``Periodontitis''}[Mesh])\ OR\ Periodontitis\ OR\ (periodontal\ disease)\ OR\ (periodontal\ disease)\ OR\ (periodontal\ disease)\ OR\ (periodontal\ disease)$

AND

<Outcome:>

<(("Glucose Metabolism Disorders" [Mesh]) OR ("Diabetes Mellitus" [Mesh]) OR (Diabetes Mellitus) OR Diabetes OR diabet* OR glucose metabolism disorders)>

AND

<(systematic review* OR meta-analysis OR meta analysis OR umbrella review*)>

The asterisk (*) was used as a truncation symbol. The search strategy was customized according to the database being searched.

Screening and selection

Screening and selection for eligible SRs was performed by three independent reviewers (EJSW, LPMW and MGPS) using the webtool Rayyan.³⁶ The reviewers first checked duplicates and subsequently checked eligibility using titles and abstracts. Based on the inclusion criteria the papers were categorized as included, excluded or undecided. During the selection process results from the reviewers were blinded. After all three reviewers completed the selection procedure the selection results were unblinded and disagreements between the reviewers was discussed. The full text SRs were obtained and used for data extraction. The most recent version of the SRs was selected after checking for updates.

Inclusion and exclusion criteria

A full-text review of relevant articles was conducted to assess the association between periodontitis and DM compared to individuals without periodontitis. Studies that met the detailed eligibility criteria were included in the analysis; the following criteria were used:

- SRs with a meta-analysis
- Full text publications available in the Dutch or English language
- SRs including data concerning human individuals, comprising two distinct groups:
 - Individuals diagnosed with periodontitis
 - Individuals without periodontitis
- Studies that primarily evaluated the presence or absence of DM (including measures such as prevalence, incidence, risk ratios (RR), odds ratios (OR), along with the corresponding 95% confidence intervals (Cl) and p-values)).

The following exclusion criteria were used:

- Other DM related parameters
- Studies that primarily focused on the effect of periodontal treatment (such as NSPT)
- Pregnancy
- Prediabetes
- Peri-implantitis
- Apical periodontitis

Data analysis

SRs that fulfilled all the above criteria were processed in this review for data extraction and analysis.

Screening and selection

This was performed by two independent reviewers (EJSW and LPMW) using a standardized data extraction form. For SRs that examined the bidirectional relationship between periodontitis and DM, only those data were extracted that evaluated periodontitis as exposure variable and DM as outcome. The following characteristics were extracted from the included SRs: focused question, search results, publication details, details on DM association and original conclusions. From the meta-analysis, the available RR or OR and the corresponding 95%CI and p-value were extracted for both random- and fixed-effects models. If both models were reported, the Cochrane guidelines were followed.³⁷ That is, if there were less than four studies included in the review, the data of the fixed-effects model were extracted. Additionally, statistical heterogeneity details such as p-values, 95%CI together with the heterogeneity test (I², Q, X² and Ri) were also extracted. At the point when an included SRs performed subgroup investigation for gender, age, smoking status, periodontitis severity and/or geographical region, the relating information was additionally extracted. As decided 'a priori' when feasible subgroup analysis on these patient- and study characteristics was performed.

Assessment of heterogeneity

The heterogeneity of the SRs was described in detail regarding the following factors:

- Clinical heterogeneity: subject characteristics, details on periodontitis and DM.
- Methodological heterogeneity: variability in review approach, risk of bias (RoB) assessment and performed analysis.

Citation Matrix

A citation matrix³⁸⁻⁴⁰ was constructed to produce a comprehensive list of unique studies within the included SRs to identify potential overlap between primary clinical studies.

Data interpretation

To interpret the magnitude of the RR the following guide was used; small, medium, and large were identified by values of >1.22, >1.86, and >3.00, respectively. 41 In addition, the ORs values of >1.68, >3.47, and >6.71 were considered indicative of small, medium and large, respectively. 42 Two methods were used to summarise the magnitude of the association: one at the level of the meta-analysis and the other at the level of the SR, for the latter a correction factor was used for the number of meta-analysis of the included studies. A p-value of p<0.05 was considered statistically significant for meta-analysis. If the p-value was not given, significance levels were interpreted based on the confidence interval.

Tests of heterogeneity resulting in a p<0.1 was considered to be statistically significant. As a guide to evaluate the potential magnitude of inconsistency among primary studies, an I^2 statistic of 0%-40% may indicate negligible levels of heterogeneity, 30%-60% may suggest moderate heterogeneity, and 50%-90% may indicate substantial heterogeneity. Furthermore, an I^2 statistic exceeding 75% was interpreted to indicate considerable heterogeneity.

Quality assessment

A list of 27 items were evaluated assigning ratings to each aspect based on the reporting and methodological quality (Online Appendix S2).³⁵ To derive an overall score for the quality assessment, positive ratings were added resulting in an overall percentage score, with a maximum score of 100% indicating that all individual items received '+' ratings when combined.^{44,45} As a guide to interpret the estimated RoB, a range of 0%-40% was interpreted

to indicate a high RoB, a range of 40%-60% a substantial RoB, a range of 60%-80% a moderate RoB, and a range of 80%-100% a low RoB. 46

Assessment of causality

In order to evaluate a potential causal association between periodontitis and DM, the Bradford-Hill criteria were applied.⁴⁷. The following nine criteria were independently evaluated (EJSW and LPMW): strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.

Grading the "body of evidence"

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system proposed by the GRADE Working Group was used to grade the evidence from this synthesis of SRs. 48-50 The quality of the evidence and the strength of the recommendations were assessed by two reviewers (EJSW and LPMW) based on several factors including study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias. For all the above discrepancies between reviewers were discussed and resolved to reach consensus and in case of continued disagreement, following discussion, a fourth reviewer (DES) made the final decision.

RESULTS

Search and selection results

Searching the MEDLINE-PubMed and Cochrane databases resulted in 487 unique papers, as illustrated in Figure 1. Screening of the titles and abstracts resulted in 26 papers, for which the full papers were obtained. The inter-rater reliability was assessed as moderate agreement between the reviewers (Cohen's kappa=0.41), the % of agreement was 96.5.⁵¹ After full-text reading 22 studies were excluded because they did not meet all eligibility criteria (for details see Appendix S1). A manual search of the reference lists did not find any additional suitable SRs. Consequently, four SRs, based on 49 primary clinical studies, were identified, and included in this review. Table 2 presents a summary of the details and characteristics of the included SRs with their IDs (I-IV).

Figure 1
Search and selection results

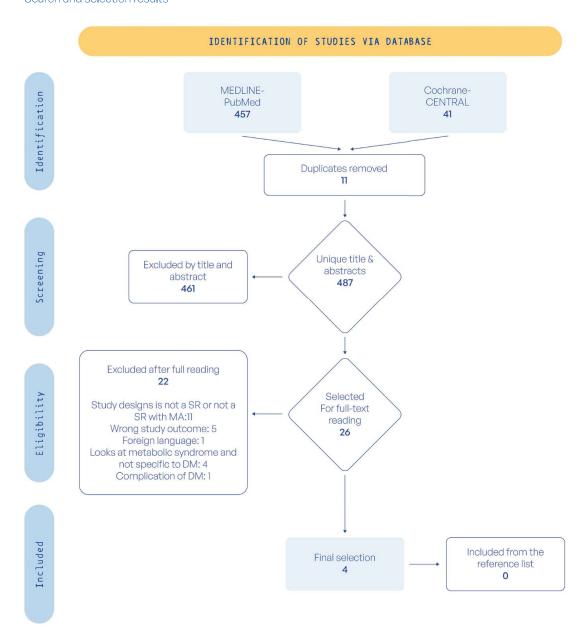


Table 2

Overview of the characteristics of the SRs included in the data extraction process.

Original conclusions of review authors review authors	"Abstract conclusion" People with moderate-to-severe cases of periodontitis have the highest risk of developing beriodontal severity on risk of periodontal severity on risk of conditions require further investigation. More homologous evidence is required to form robust conclusions regarding periodontitis-multimorbidity - Critical RoB was mainly associated with confounding and selection bias. - On the basis of the GRADE criteria, the certainty of the evidence in this SR was low to very low. - The study was supported by a Frederick E. Hopper Scholarship at the university of Leeds.	"Abstract conclusion" The findings show a positive bidirectional association between periodontal disease and diabetes mellitus, and thus, underline the need for screening of patients with periodontitis regarding with periodontitis regarding small number of studies.
Leading mode of analysis	DA + MA	DA + MA
Number of included studies/trails N= involved participants DM	10 studies (DA:10 and MA: 9) N= 442,920 \$ DM type I/II	10 studies N= 427,620 DM type I/II
Data bases searched	o MEDLINE o Cochrane o EMBASE	o PubMed o Web of Science
Author (year) RoB (%) (Online Appendix S2)	I: Larvin et al. 2022 ⁶² RoB: Moderate (78%)	II: Stöhr et al. 2021 ⁶³ RoB: Low (89%)

- The included studies had an observational study design, so residual confounding cannot be ruled out. - Grey literature was not searched for as part of the study. - There is significant heterogeneity across studies.	 In this study data were pooled and a meta-analysis was performed, although there was heterogeneity between the studies. Sub-analyses should be treated with caution because these are based on a small number of studies. The study was supported by National Nature Science Foundation of China, Key Technology R&D program of Sichuan Province of China and Graduate Student's research and Innovation Fund of Sichuan University.
	"Abstract conclusion" There is an evident bidirectional relationship between T2DM and periodontitis. Further welldesigned cohort studies are needed to confirm this finding. Our results suggest that both dentists and physicians need to be aware of the strong connection between periodontitis and T2DM. Controlling these two diseases might help prevent each other's incidence.
	DA H
	I3 studies N= 43,614 ◊ DM type II
	o MEDLINE- PubMed o EMBASE o Chinese BioMedical Literature Database (CBM) o China National Knowledge Infrastructure (CNKI)
	III: Wu et al. 2020 ⁵⁴ ROB: Low (85%)

IV: Ziukaite et al. 2018 ⁵⁵	o PubMed- MEDLINE	27 studies	DA + MA	"Abstract conclusion" The overall prevalence and odds	- The study findings suggest the presence of publication
RoB: Low (81%)	o Cochrane- CENTRAL	N= 83,340		of having diabetes are higher within periodontitis populations	bias The included papers used
	o EMBASE	DM type I/II		compared to people without	different definitions of
				diabetes	methods of classifying DM.
				underestimates the prevalence	
				when compared to this condition	
				assessed clinically. Geographical	
				differences were observed: the	
				highest diabetes prevalence	
				among subjects with periodontitis	
				was observed in studies	
				conducted in Asia and the lowest	
				in studies originating from Europe.	

Abbreviations: Cl, confidence interval; DA, descriptive analysis; DM, Diabetes Mellitus; EBM, Evidence Based Medicine; GRADE, Grading of recommendations assessment, development, and evaluation; HbA1c, glycated haemoglobin; I², Higgins test for heterogeneity; RoB, Risk of bias; RR, Relative risk; SR, Systematic review; SRR, summary relative risk; Type II DM, Type 2 diabetes mellitus; Ø, The synthesis researchers calculated the number of people; I + II, both type I and II separate; I/II, Type I and II grouped or merged.

Assessment of heterogeneity

The four included SRs demonstrated heterogeneity of the characteristics of the primary studies and their subjects, details regarding periodontitis and DM, inclusion and exclusion criteria, searched databases, quality assessment scales employed, as well as the aims, methods of recording and reporting and presence of meta-analysis (Table 2).

Assessment of citations

There was an overlap in the inclusion of primary clinical studies across multiple SRs, as some SRs incorporated the same clinical studies in their analysis (Online Appendix S3).

Quality assessment

The assessment involved critically evaluating 27 items, including the focused question, registration and 'a priori' development of a protocol, presentation of eligibility criteria, variety of databases or additional sources searched, inclusion of non-English-language literature, details on the study selection process, grading of the obtained evidence and assessment of publication bias. The included SRs were assessed as having a low to moderate estimated RoB as shown in Table 2 and Online Appendix S2.

SR outcome results

Four SRs (I⁵², II⁵³, III⁵⁴, IV⁵⁵) were used to investigate the relationship between DM and periodontitis. The specifics of the data extracted from the meta-analysis are presented in Table 3A and Table 4. Details about the included studies can be found in Online Appendix S4. All included reviews revealed a relationship, indicating an elevated risk of DM for patients with periodontitis compared to those without. The meta-analysis in the included papers showed a statistically significant association between periodontitis and DM which were estimated ^{41,42} to reflect a medium magnitude for 14% of the outcomes and 57% showed a small association. In 29% the magnitude of the association was estimated to be negligible. Based on the findings of the meta-analysis, it appears that the statistical heterogeneity among the included primary studies range from potentially not important to substantial (Table 3A).

Subgroup analysis

All four SRs (I⁵², II⁵³, III⁵⁴, IV⁵⁵) performed subgroup analyses evaluating the association of periodontitis and DM relative to parameters for gender, periodontitis severity, smoking and geographical region. None of the included SRs have performed a subgroup-analysis on the association of periodontitis and DM relative to age. Only SR IV⁵⁵ limited their study population for those who were over the age of 18. Data and details for subgroup-analyses from the included SRs are shown in Table 3B.

Gender

One SR (II⁵³) evaluated the association of periodontitis and DM relative to gender suggesting a higher risk in woman with a RR of 2.00 (95%CI=1.58-2.54; I²=0.0%, p=0.974) compared to for men (RR= 1.31, 95%CI=1.01-1.70; I²=58%, p=0.048). Interpreting the RRs the magnitude of association was estimated to be small.⁴¹ Assessment of heterogeneity with one included SR was not applicable.

Periodontitis severity

Two SRs (I⁵², III⁵⁴) evaluated the association of periodontitis and DM in relation to periodontitis severity. The findings suggest that periodontitis severity may play a role in the association between periodontitis and DM, with individuals with severe periodontitis experiencing a significantly higher risk.

SR I⁵² distinguished between moderate and severe periodontitis for analysis. Patients with moderate periodontitis had a 20% significant higher risk of incident DM compared to healthy controls, while patients with severe periodontitis had a 34% significant higher risk compared to healthy controls. SR (III⁵⁴) confirmed these findings by meta-analysis showing a 28% higher risk of developing type II DM in people with mild periodontitis (RR=1.28, 95%Cl=1.07–1.54, p=0.007) and in 53% for severe periodontitis (RR=1.53, 95%Cl=1.27-1.83, p=0.000) compared to healthy controls. The magnitude of the association with the observed RR can be estimated as none to small.⁴¹ The statistical heterogeneity as emerging from the meta-analysis was low among the included primary studies (I²=0%; I²=20.1%; Table 3B).

Smoking status

One SR (II)⁵³ evaluated the association of periodontitis and DM relative to the smoking status. People with periodontitis who had ever smoked had a significant 28% higher risk of DM compared to those that were non-smokers (RR=1.28, 95%Cl=1.10-1.66). Interpreting the RRs the magnitude of association was considered as small. The heterogeneity was substantial (I2=87%, p=0.033). In those who had never smoked, there was also a significant difference (RR=1.39, 95%Cl=1.10-1.76) between people with periodontitis and non-periodontitis in association with DM. The analysis for heterogeneity (I²) between the people that never smoked compared to people that had a history of smoking was not significant (p=0.718). These data should be treated with caution due to the limited primary studies included.

Geographical region

Two SRs (I⁵², III⁵⁴) evaluated the association of periodontitis and DM in relation to geographical region where the primary study was performed. SR II⁵³ made a distinction between the geographical regions Asia, Europe and the USA. For Asia and the USA, the association was significant, respectively RR=1.19 (95%CI=1.09-1.30) and RR=1.61 (95%CI=1.34-1.94). No significant association was found for Europe. This was confirmed by study IV⁵⁵ showing the highest prevalence of DM in Asia (17.2%), followed by South America (11.9%) and North America (10.3%), with the lowest prevalence in Europe (4.3%). Following this, the meta-analysis estimated the OR for individuals with periodontitis to have DM. The ORs were 1.99 in Asia (95%CI=1.66-2.39, p<.00001), 4.63 for South America (95%CI=2.76-7.76, p<.00001), 2.21 for North America (95%CI=1.87-2.60, p<.00001) and 2.77 for Europe (95%CI=1.31-5.87, p=0.008). For details see Table 3B. Additionally, interpreting the extracted ORs and RRs shows that the magnitude of the association ranges from none to small for the RR and small to large for the OR. Heterogeneity varied from potentially not important to considerable (For details see Table 3B).

 $\begin{tabular}{ll} \textbf{Table 3A} \\ \textbf{Summary of data extraction for the included SRs with DM outcomes.} \\ \end{tabular}$

Source					Outcome		Heterogeneity	eneity
Disease or event	SR	No. studies in MA (variable)	No. patients in MA	Effect model (Fixed/ Random): OR/ RR*	12%26	p value	I², Q*, X²**, Ri***	p value
		9 (total)	418,821 (Random 1.22*	1.13 - 1.33	Sign ◊, p=NR	53.8%	0.02
	52	8 (Clinical periodontitis)	416,352 (Random 1.16*	1.10 – 1.22	Sign ◊, p=NR	20.3%	0.10
	1153	10 (total)	427,620	Random 1.26*	1.12 – 1.41	Sign ◊, p=NR	70.8%	0.000
DM	III54	3 (total Type II DM prevalence)	9961	Random 4.04	2.48 - 6.59	0.000	0.0%	1.000
		16 (total)	73,973 (Random 2.27	1.90 – 2.72	<.00001	74%	<.00000
	1\square 22	7 (self-reported DM)	16,358 ()	Random 2.92	2.00 - 4.26	<.00001	47%	0.08
		8 (clinically assessed DM)	57,162 (Random 1.82	1.55 - 2.13	<.00001	%09	<.01

Table 3B

Summary of data extraction for the included SRs for subgroup analysis.

Source				Outcome			Heterogeneity	eneity
Subgroup analysis	SR	No. studies in MA (variable)	No. patients in MA	Effect model (Fixed/ Random): OR/ RR*	95%CI	p value	7. Q*, X2*, Ri***	p value
300	1153	5 (men)	خ	Random 1.31*	1.01 – 1.70	Sign ◊, p=NR	28%	0.048
Gerider		2 (women)	خ	Random 2.00*	1.58 - 2.54	Sign ◊, p=NR	%0.0	0.974
	152	6 (moderate periodontitis)	56,823 (Random 1.20*	1.11 – 1.31	Sign ◊, p=NR	%0.0	0.46
	<u>-</u>	5 (Severe periodontitis)	8,048 (Random 1.34*	1.10 – 1.63	Sign ◊, p=NR	20.1%	0.24
Periodontitis severity	 54	7 (mild periodontitis on type II DM incidence)	8701	Random 1.28*	1.07 – 1.54	0.007	20.4%	0.274
		7 (Severe periodontitis on type II DM incidence)	3994	Random 1.53*	1.27 - 1.83	0.000	%0.0	0.649
Smoking	153	3 (never)	خ	Random 1.39*	1.10 – 1.76	Sign ◊, p=NR	7%	0.340
status	 }_	2 (ever)	5	Random 1.28*	1.10 – 1.66	Sign ◊, p=NR	78%	0.033
		5 (Asia)	خ	Random 1.19*	1.09 – 1.30	Sign ◊, p=NR	22%	0.063
	<u> </u> 53	2 (USA)	خ	Random 1.61*	1.34 - 1.94	Sign ◊, p=NR	%0	0.535
		3 (Europe)	C·	Random 1.20*	0.72 – 1.99	Not-Sign ◊, p=NR	78%	0.012
Geographical		8 (Asia)	57,735 (Random 1.99	1.66 - 2.39	<.00001	72%	0.0000
lioibei	17 755	1 (Australia)	310 (Random 14.22	0.86 - 235.97	no M∠	no MA, N=1	
		2 (Europe)	1384 (Fixed 2.77	1.31 - 5.87	0.008	%0	0.34
		2 (North America)	13007 (Fixed 2.21	1.87 – 2.60	<.00001	17%	0.27
		3 (South America)	1537 ◊	Fixed 4.63	2.76 – 7.76	<.00001	%0	0.62

Abbreviations: ?, unknown; Cl, confidence interval; DM, Diabetes Mellitus; I², Higgins test for heterogeneity; MA, meta-analysis; NR, Not reported; OR, Odds Ratio; Q*, Cochran's Q test for heterogeneity; RR, Relative risk; RR*, Relative Risk; Sign; significant; SR, Systematic review; X***, Chi-square test for heterogeneity; Q, The synthesis researchers calculated or judged these themself.

Legends table 3a and 3b

Large RR 3.00
Medium RR 1.86
Small RR1.22
None RR 0
Meta-analysis outcome (RR)

As a guideline, RR magnitude of association was interpreted using a normal standard deviation. Values of >1.22, >1.86, and >3.00 were considered to indicate small, medium, and large magnitudes, respectively.4

As a guideline, OR magnitude of association was interpreted using a normal standard deviation. Values of >1.68, >3.47, and >6.71 were considered indicative of small, medium, and large magnitudes, respectively.42

Significant	Meta-analyses outcomes:	p<0.05
Not cianificant		Meta-analyses outconnes. p≥0.05
Significance		(b)

The results of meta-analyses that resulted in a p<0.05 were considered to be statistically significant.

Considerable 75-100%
Substantial 50–90%
Moderate 30–60%
Potential not important 0-40%
Test of heterogeneity (I ²)

As a guideline for evaluating the potential inconsistency between studies, an P statistic of 0%-40% may indicate unimportant levels of heterogeneity, 30%-60% may suggest moderate heterogeneity, 50%-90% may represent substantial heterogeneity. An P statistic of greater than 75% was interpreted to indicate considerable heterogeneity.43

Table 4ASummary of the magnitude of association for the extracted RRs and ORs related to DM.

DM							
	Total number Number of Magnitude of the extracted RRs ⁴¹ and ORs ⁴					d ORs ⁴²	
SR	of included studies	performed MAs	None	Small	Medium	Large	
52	9	2	2/2				
⁵³	10	1	1 1/1				
III ⁵⁴	3	1 1/1					
IV ⁵⁵	16	3 3/3					
Summary	Summary 7 2/7 = 29% 4/7 = 57% 1/7 = 14% 0%						
Overall	Of the 7 performed meta-analysis, 14% of the values of the RRs and the ORs show a medium magnitude of association between periodontitis and DM. The biggest part (57%) showed a small association of periodontitis and DM. At last, 29% showed a neglectable association.						

Abbreviations: DM, Diabetes Mellitus; MAs, meta-analyses; OR, Odds Ratio; RR, Relative risk; SR, Systematic review.

Table 4B

Summary of the magnitude of association for the extracted RRs and ORs related to DM. With a correction factor of the number of meta-analyses per included study.

DM							
	Total number Number of ext				gnitude of association for the extracted RRs ⁴¹ and ORs ⁴²		
SR	of included studies	performed MAs	None	Small	Medium	Large	
 52	9	2 2/2					
⁵³	10	1 1/1					
⁵⁴	3	1 1/1					
IV ⁵⁵	16	3	3/3				
Summary 1/4 = 25% 2/4 = 50% 1/4 = 25% 0%							
Overall	Of the 4 SRs that performed meta-analysis, the majority (50%) of the values of the RRs and the ORs showed a small magnitude of association between periodontitis and DM.						

 $Abbreviations: DM, Diabetes \, Mellitus; \, MAs, \, meta-analyses; \, OR, \, Odds \, Ratio; \, RR, \, Relative \, risk; \, SR, \, Systematic \, review.$

Assessment of causality

Table 5 summarizes the application of the Bradford Hill criteria (for detailed explanation see online appendix S5). Of the nine Bradford Hill criteria⁴⁷, only three criteria including consistency, biological gradient, and plausibility were fulfilled.

Table 5

Summary of Bradford Hill criteria⁴⁷ for causality.

;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	DM	1	()
Oriteria	Meaning	Yes	No	Motivation
Strength of association (Table 3)	A strong association is more likely to have a causal component than is modest association. Strength of the association is determined by the types of existing studies. The highest-level studies from the evidence pyramid would represent the strongest associations (i.e., RCTs and SRs with meta-analyses). Results from these studies must demonstrate an OR or RR of at least 2.0 or above in order to be meaningful. Anything between 1 and 2 is weak while >2 is moderate and >4 is considered strong.		×	Table 3A - 4/7 MAs showed an OR or RR between 1.0 and 2.0 - 3/7 MAs showed an OR or RR above 2.0 - Greatest OR is 4.04.
Consistency	A relationship is repeatedly observed in all available studies.	×		Table 3A All MAs showed significant results based on significant p-values or 95% confidence intervals with a OR or RR above 1.0
Specificity	A factor influences specifically a particular outcome or population. The more specific an association between a factor and an effect, the greater the probability that it is causal.		×	All SRs examine the association of periodontitis and DM related outcomes. However, not all SRs did report the same outcome in every instance.
Temporality	The cause must precede the outcome it is assumed to affect (e.g., smoking before the appearance of lung cancer). Outcome measured over time (longitudinal study).		×	Based on the included SRs, temporality could not be established
Biological gradient (dose- response)	The outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory (e.g., the more cigarettes one smokes, the greater the chance of the cancer occurring).		×	Only two of the four studies focused on periodontitis severity and the risk of developing DM.

Plausibility	The observed association can be plausibly explained by substantive matter (i.e., biologically possible).	×		The presence of untreated periodontitis is known to cause chronic inflammation. This chronic inflammatory state is associated with insulin resistance, which worsens glycaemia control.
Coherence	A causal conclusion should not fundamentally contradict present substantive knowledge. Studies must not contradict each other.	×		Many previous studies showed the relationship between periodontitis and DM, as well as this synthesis. However, this synthesis of SRs suggests a mostly negligible to small magnitude of association between periodontitis and DM, challenging the more assertive claims made in previous studies.
Experiment	Causation is more likely if evidence is based on randomized experiments or a systematic review of randomized experiments. However, RCTs may not be ethically possible and thus prospective rather than experimental studies, such as cohort studies, may be the highest level of evidence available.	ΑN	∀ Z	This criterion does not apply to this synthesis as randomized controlled trials (RCTs) for this synthesis cannot be obtained ethically.
Analogy	For analogous exposures & outcomes an effect has already been shown (e.g., Effects first demonstrated on animals or an effect previously occurring on humans such as the effects of thalidomide on a fetus during pregnancy).	∀ Z	Ą Z	This criterion does not apply to this synthesis as it was not investigated as animal studies were excluded from this study.

Abbreviations: DM, Diabetes Mellitus; MAs, meta-analyses; NA, not applicable; OR, Odds ratio; RCT, Randomized controlled trial; RR, Relative risk; SR, Systematic review.

Evidence profile

Table 6 summarize the body of evidence, and the strength of recommendations as assessed by GRADE. 48-50 The four SRs examined demonstrated a potential risk of bias from low to moderate (see Table 2, Online Appendix S2). Data from the primary studies were derived from different populations and continents. Therefore, these findings are considered to be generalizable. Based on the heterogeneity between the included SRs, data were judged to be rather inconsistent (presented in Table 3A). The data were considered to be rather precise because all selected SRs focussed on DM related outcomes and because all SRs revealed a result based on p-value or the 95%CI (Table 3A). As publication bias may have been present, the presence of reporting bias is likely. The magnitude of the association is interpreted as a negligible to small (see Table 3A, 3B, 4A, 4B). Considering all GRADE aspects, the evidence profile that emerges from this synthesis is that there is a moderate level of certainty that the magnitude of association a of periodontitis population compared to a non-periodontitis population with DM is negligible to small.

Table 6Estimated evidence profile (GRADE)⁴⁸⁻⁵⁰ for the association of periodontitis and various DM parameters.

GRADE	DM		
Study designs	SRs N= 4		
Reporting and methodological estimated potential risk of bias (Online Appendix S2)	Low to moderate		
Consistency (Table 3A)	Rather inconsistent		
Heterogeneity (Table 2)	Clinical and methodological heterogeneity		
Directness	Rather generalizable		
Precision (Table 3A, 3B)	Rather precise		
Publication bias	Likely		
Magnitude of the association ^{41, 42} (Table 3A, 3B, 4A, 4B)	Small		
Certainty	Moderate		
Bradford Hill Criteria	Uncertain Causal Relationship		
Summary and direction of the findings	There was a moderate level of certainty that the magnitude of the association of DM with periodontitis is negligible to small.		

Abbreviations: DM, Diabetes Mellitus; OR Odds ratio;; RR, Relative risk; SR, Systematic review.

DISCUSSION

Summary of the findings

This synopsis of synthesis aimed to consolidate the existing dental and medical literature from SRs regarding the magnitude of the association between periodontitis and presence or absence of DM. SRs were prioritized due to their comprehensive nature, offering a stronger body of evidence compared to individual clinical studies. Analysis of the four SRs incorporated in this review consistently indicated a significant association of DM in patients with periodontitis compared to those without (Table 3A). However, the magnitude of this association was generally estimated to be negligible to small (Table 4A and 4B). Both the statistical significance and magnitude of the association varied, affected by factors such as gender, age, the severity of periodontitis, smoking status, and geographic location, which may impact the link between periodontitis and the presence or absence of DM (Table 3B). It is important to acknowledge the heterogeneity observed across the included clinical studies, making direct comparison of the SRs challenging due to discrepancies in the methodologies used to assess the relationship. Furthermore, these findings should be interpreted with caution due to the potential bias in the data derived from the included SRs.

The association between periodontitis and DM

Periodontitis affects alycaemic control and contributes to the progression of DM. It can lead to insulin resistance, making it more challenging to regulate blood sugar levels. Moreover, the systemic dissemination of inflammatory mediators from periodontal tissues can exacerbate systemic inflammation, further worsening insulin sensitivity and glycemic control in DM.56 Conversely, particularly poorly controlled DM, is considered a significant risk factor for the development and progression of periodontitis. 57,58 Elevated blood sugar levels in DM can lead to changes in the oral microbiome, favoring the growth of periodontal pathogens. Additionally, DM compromises the immune response, impairing the body's ability to combat oral infections such as periodontitis. This may result in increased susceptibility to periodontal tissue inflammation and impairement.⁵⁶ Both conditions also share common pathogenic mechanisms, including inflammation, oxidative stress, and dysregulated immune responses. These mechanisms collectively contribute to the onset and progression of both diseases.¹⁸ The direct relationship is complex, highlighting the multifaceted nature of these conditions.²⁵ Additionally, shared risk factors such as smoking, obesity, and genetic predisposition further contribute to the interplay between DM and periodontitis.⁵⁹ The bidirectional relationship has been highlighted in the literature over the last two decades. 13,14,60,61 The overall evidence emerging from this MR suggests a negligible to small association between periodontitis and DM (Table 4A and 4B) but does not establish a direct causal relationship (Table 6, Online Appendix S5).

Individual factors contributing the association

Factors such as gender, age, periodontitis severity, smoking status and/or study region could contribute to the periodontitis-DM relationship. The included SRs conducted subanalyses regarding these factors.

Previous studies have shown hormonal variations and lifestyle factors contribute to gender-related differences in the association between periodontitis and DM.⁶²⁻⁶⁴ SR (II⁵³) found in patients with periodontitis a higher risk for DM related outcomes in women (RR=2.00) compared to men (RR=1.31). It is important to note that these findings are based on limited evidence since only two clinical studies were included for the meta-analysis regarding the association between the female gender, periodontitis, and DM.⁵³ The possible role of hormonal

fluctuations, particularly oestrogen and progesterone in women, could be explained by changes in the immune response. It may affect the severity and progression of both periodontitis and DM differently in woman compared to men. In contrast, previous studies in US adults have reported that the prevalence of DM is higher in males than females by only 1.6%, while the prevalence of moderate-severe periodontitis in US adults is much higher in males then in females, 11.95% higher in NHANES 2009–2014. The gender-dependent association between type II DM and moderate-severe periodontitis only existed in males and not in females. Findings regarding the influence of gender on the association between periodontitis and DM are still inconsistent.

This synthesis does not include any SRs that have evaluated age, which therefore does not allow for substantiation of these results. Several studies have shown that aging is a significant factor in both type II DM and the risk of developing periodontitis. ⁶⁶ Moreover, older age is linked to a higher risk and longer duration of DM, both of which are associated with an increased risk of severe periodontitis. ^{18,64}. It is worth noting that periodontitis is one of many conditions that becomes more prevalent with age. Aging is strongly associated with the development of chronic diseases and age-related health conditions, which negatively impact the health and quality of life of older people. ⁶⁷

Smoking is a well-established risk factor for both periodontitis and DM by worsening the loss of periodontal tissues and complicating the treatment of DM. ^{23,25,68} Moreover, inadequately controlled DM is recognized as a risk factor for periodontitis, alongside smoking. ^{17,25} One SR (II⁵³) found a 28% higher risk of developing DM for periodontitis individuals who had a history of smoking. Smokers with periodontitis should be aware of the potential increased risk of DM and take active measures to control their DM risk factors, including smoking cessation. However, is important to note that these findings are based on only one SR (including five studies) to support their conclusions and should therefore be interpreted with caution.

The emerging evidence for this MR suggests a small to medium influence of the geographic area of origin on the observed risk of DM in patients with periodontitis (II⁵³, IV⁵⁵). Subgroup analyses showed significant higher outcomes for DM in people with periodontitis from Asia and the USA (II⁵³). Asians are particularly susceptible to periodontitis and DM⁶⁹ is found to be more prevalent compared to other ethnic groups.^{70,71} This was also confirmed by one SR (IV⁵⁵) finding higher prevalence in Asia (17.2%), followed by South America (11.9%) and North America (10.3%). Europe reported the lowest prevalence (4.3%). However, all clinical studies that focused on Europe presented data about self-reported DM. It is known that the use of self-reported data has a lower sensitivity compared to clinical assessments.⁷² Moreover, higher values were also found for self-reported DM (OR=2.92) compared to clinically assessed (OR=1.82). The lower estimates based on participants' self-reports, compared to clinically measured data, might suggest an underestimation. It should also be noted that there was substantial heterogeneity for especially the Asian studies. Therefore, all findings should be interpreted with caution.

In summary, the sub-analyses showed that certain factors, such as gender, severity of periodontitis, smoking status, and geographical location can influence the association, but it is still unclear to what extent these factors affect the relationship between periodontitis and DM.

Interpretation of the magnitude of the association

Table 4A and 4B summarizes the magnitude of association for both RRs and ORs from Table 3A, offering an overview of the most frequent reported magnitude of association. It is important to be critical of the interpretative values and to recognize the limitations of providing a simplified summary of the dispersion and magnitude of association. Rosenthal J.A. (1996)⁷³ highlights the role of magnitude of association in providing benchmarks for comparing observed values

with known norms.⁷³ Empirically derived guidelines emphasise the importance of magnitude of association in assessing the practical relevance of identified associations.^{41,74} However, challenges such as publication bias and the small study effect may influence the interpretation of magnitude of association.⁷⁴ Magnitudes of association, whether small, medium, or large, contribute to a comprehensive understanding of the direction and magnitude of a variable, beyond the limitations of p-values alone.⁴¹ ORs are widely used in epidemiological studies, but care should be taken not to confuse statistical significance with the magnitude of the association.⁴² The difference between statistical significance and magnitude of association is crucial, as a large sample size can make even weak associations statistically significant.⁴² Table 4 shows that the magnitudes of association vary from none to medium, with most of them showing a small association. This small magnitude of association highlights the need for careful interpretation of the statistical significance observed between periodontitis and DM. Reporting the magnitude of association is essential to indicate the practical significance of findings, facilitate comparisons between studies, and guide future research.

Citation matrix

When conducting a MR, it is important to examine the primary studies across multiple SRs to assess the degree of overlap³⁹. The degree of overlap indicates whether reviews cover the same or different literature from primary studies. To address this, a citation matrix was prepared to provide a comprehensive overview of the primary studies included in the underlying SRs. The primary studies that overlap in most SRs are Demmer et al. 2008, Ide et al. 2011, Miyawaki et al. 2016, Winning et al. 2017, Kebede et al. 2018, Myllymäki et al. 2018 and Morita et al. 2012, which were included in three of the four SRs identified, with publication dates between 2018 to 2022.^{75–81} Those studies were of considerable epidemiological scale, included a substantial number of participants or had a long-term follow-up period. Overlap of these primary studies may suggest that these studies provide valuable, reliable evidence in investigating the possible link between periodontitis and DM.^{38–40}

However, overlap has also the potential to artificially inflate the accuracy of the analysis by overestimating the sample size and events. Including the same study multiple times in an analysis could influence the results and unwarranted weight ^{38–40}. The complexity of this problem is highlighted by the lack of a standardized approach to dealing with overlap, which varies depending on literature trends, yields, and the scope of the review question. Furthermore, the absence of overlap between studies can be attributed to differences in inclusion and exclusion criteria, search strategies, and databases.

Appraisal of the evidence

The application of the Bradford Hill criteria ⁴⁷ for causality to assess the association between periodontitis and DM is shown in Table 5 and Online Appendix S5. It should be noted that not all of the Bradford Hill criteria could be met due to ethical reasons and the exclusion criteria of this study. Therefore, the criteria of experiment and analogy were not applicable, which limited the assessment of causality. The table shows the strength of the association, but notes that this does not provide definitive evidence of causality of periodontitis on DM. During the evaluation of the checklist, it was observed that a biological gradient (dose-response) could be present based on the synthesis of only two included SRs (I⁵², III⁵⁴, Table 3B). However, due to the limited number of SRs that invested this sub-analysis, it was not possible to conclude that a true dose-response relationship exists. Therefore, this criterion was set to 'no' regardless. Furthermore, to address the 'strength of association' box, the authors considered the answer to be 'not present' as more than 50% (4 out of 7 meta-analysis) showed an OR or RR between

one and two. However, it is worth noting that two analyses showed an OR higher than two and one analysis showed an OR higher than four, indicating a stronger association (Table 3A). There seems to be a conflict in interpretation and application of rated evidence. For instance, an OR of 1.82 is considered as "small". 41,42 But as these were below 2 according to the Bradford Hill criteria it is considered as "no". This vacuum of interpretation applies for all OR between 1.68 and 2 and all RR between 1.22 and 2. In order to overcome this there is a need to have international alignment between groups like, scientists, epidemiologists, statisticians and clinicians.

Limitations

It is important to acknowledge that this MR has several limitations that affect the interpretation of the conclusions.

- One major limitation is the heterogeneity of the included SRs. This heterogeneity includes variations in the characteristics of the populations studied, inclusion and exclusion criteria, databases used, quality assessment scales, and various methods used to assess periodontitis and DM (Table 2). Direct comparisons between different SRs were difficult due to the diversity in approach and measurement instruments.
- The quality and potential bias of the primary studies included in the SRs also posed a challenge. Small sample sizes, lack of longitudinal data, and insufficient control for confounding variables may affect the strength of the conclusions. Methodological quality and bias are important factors in drawing accurate conclusions from a study.³⁸
- Longitudinal and experimental data are often not possible, limiting the ability to infer causality. Observational research, which is often used in primary studies of the included SRs, can demonstrate associations but cannot establish causal relationships.⁸²
- Two SRs were excluded based on full-text reading because they did not have a meta-analysis. The conclusions of these two excluded SRs are in the same direction as the conclusion of the meta-analysis presented in this synthesis. The SR of Borgnakke et al. (2013)⁵⁷ concluded that there is evidence suggesting that people with poor periodontal health and no DM have a greater risk of developing manifest DM than people with good periodontal health. The second SR of Graziani et al. (2018)⁵⁸ is an updated version of SR of Borgnakke⁵⁷ and aimed to review the relationship between periodontitis and glycaemic control, DM complications, and DM incidence.

Directions for future research

Further studies are required to establish causality between periodontitis and DM and investigate underlying mechanisms. Future research should also aim to standardize definitions and assessment methods for periodontitis and DM to facilitate comparison and synthesis of studies.

CONCLUSION

Based on the quality of the evidence this MR of SRs shows that there is moderate certainty that the magnitude of association of a periodontitis population compared to a non-periodontitis population with DM is negligible to small. Causality could not be established. Factors such as gender, periodontitis severity, smoking status, and geographical region appeared to have an impact on the association. This should be treated with caution due to the limited primary studies included. This nuanced understanding underscores the complexity of the potential relationship and emphasizes the need for ongoing exploration in future research.

CLINICAL RELEVANCE

Scientific rationale for this analysis

This synthesis focussed on the association between periodontitis and DM. There is increasing global prevalence of both conditions. Understanding the potential association is important for developing effective treatment strategies and preventive measures.

Principle findings

The synthesis indicates with moderate level of confidence for a negligible to small association between DM and periodontitis as compared to the non-periodontitis population. However, the available evidence did not support a causal relationship.

Practical implications

In absence of a potential association, it remains important to maintaining good oral health for overall well-being, as periodontitis can also negatively affect quality of life.

Online Appendices



STATEMENTS

Acknowledgements

The authors acknowledge the support of Joost Bouwman, head librarian of the Academic Centre for Dentistry Amsterdam, who helped in the retrieval of the full-text articles.

Statement of ethics

This research has been approved by the ACTA Institutional review board, by reference number 2022-48457 and registered at the International Prospective Register of Systematic Reviews (PROSPERO) by number CRD42024512767

Conflict of interest statement

The first author and co-authors declare that they have no conflicts of interest.

Funding sources

This paper was prepared as part of the obligation of one of the first authors to fulfil the requirements of the ACTA Master's program in dentistry. This review was self-funded by the authors and the institution.

Data statement

More detailed data that support the findings of this study are included in this article and the onlince appendice. Further enquiries can be directed to the corresponding author.

Author contributions

EJSW: contributed to conception and design, search and selection, analysis and interpretation, and drafted the manuscript.

LPMW: contributed to conception and design, search and selection, analysis and interpretation, and drafted the manuscript.

MGPS: contributed to search and selection and critically revised the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

REFERENCES

The papers included in this synthesis are highlighted in **bold** in the list.

- World Health Organization. Diabetes. Accessed 5 April 2023. https://www.who.int/news-room/fact-sheets/detail/diabetes
- 2. World Health Organization. Classification of diabetes mellitus. 2019. Accessed 5 April 2023. https://www.who.int/publications/i/item/classification-of-diabetes-mellitus
- 3. Nibali L, Gkranias N, Mainas G, Di Pino A. Periodontitis and implant complications in diabetes. *Periodontol 2000*. 2022;90(1):88-105. doi:10.1111/prd.12451
- 4. Chapple ILC, Bouchard P, Cagetti MG, et al. Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: consensus report of group 2 of the joint workshop on the boundaries between caries and periodontal diseases. *J Clin Periodontol*. 2017;44(S18):S39-S51. doi:10.1111/jope.12685
- 5. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843. doi:10.1016/j.diabres.2019.107843
- 6. Sanz M, D'Aiuto F, Deanfield J, Fernandez-Aviles F. European workshop in periodontal health and cardiovascular disease-scientific evidence on the association between periodontal and cardiovascular diseases: a review of the literature. European Heart Journal Supplements. 2010;12(Suppl B):B3-B12. doi:10.1093/eurheartj/suq003
- 7. Kassebaum NJ, Smith AGC, Bernabé E, et al. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990–2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. J Dent Res. 2017;96(4):380–387. doi:10.1177/0022034517693566
- 8. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global Burden of Severe Periodontitis in 1990-2010. *J Dent Res.* 2014;93(11):1045-1053. doi:10.1177/0022034514552491
- 9. van der Velden U. 5 Classificatie van parodontitis. In: *Parodontologie*. Bohn Stafleu van Loghum; 2009:51-53. doi:10.1007/978-90-313-6887-7 5
- 10. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri Implant Diseases and Conditions. *J Periodontol*. 2018;89(S1):S173-S182. doi:10.1002/JPER.17-0721
- 11. Chapple ILC, Van der Weijden F, Doerfer C, et al. Primary prevention of periodontitis: managing gingivitis. *J Clin Periodontol.* 2015;42(S16):S71–S76. doi:10.1111/jcpe.12366
- 12. Herrera D, Sanz M, Shapira L, et al. Association between periodontal diseases and cardiovascular diseases, diabetes and respiratory diseases: Consensus report of the Joint Workshop by the European Federation of Periodontology (EFP) and the European arm of the World Organization of Family Doc. *J Clin Periodontol*. 2023;50(6):819-841. doi:10.1111/icpe.13807
- 13. Kuo LC, Polson AM, Kang T. Associations between periodontal diseases and systemic diseases: A review of the inter-relationships and interactions with diabetes, respiratory diseases, cardiovascular diseases and osteoporosis. *Public Health*. 2008;122(4):417-433. doi:10.1016/j.puhe.2007.07.004
- 14. Santos Tunes R, Foss-Freitas MC, Nogueira-Filho G da R. Impact of periodontitis on the diabetes-related inflammatory status. *J Can Dent Assoc.* 2010;76:a35.
- 15. Löe H. Periodontal Disease: The sixth complication of diabetes mellitus. *Diabetes Care.* 1993;16(1):329-334. doi:10.2337/diacare.16.1.329
- Weijdijk LPM, Ziukaite L, Van der Weijden GA, Bakker EWP, Slot DE. The risk of tooth loss in patients with diabetes: A systematic review and meta-analysis. Int J Dent Hyg. 2022;20(1):145-166. doi:10.1111/idh.12512
- 17. van Strydonc DAC, Katsamakis S, van der Weijden GA. *Parodontale Screening, Diagnostiek En Behandeling in de Algemene Praktijk*.; 2020.
- 18. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. *Nat Rev Endocrinol*. 2011;7(12):738-748. doi:10.1038/nrendo.2011.106
- 19. Chapple ILC, Genco R. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol*. 2013;84(4S). doi:10.1902/jop.2013.1340011
- 20. Chávarry NGM, Vettore MV, Sansone C, Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. *Oral Health Prev Dent.* 2009;7(2):107-127.
- 21. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. *J Diabetes Complications*. 2006;20(1):59-68. doi:10.1016/j.jdiacomp.2005.05.006
- 22. Mealey BL, Oates TW. Diabetes Mellitus and Periodontal Diseases. *J Periodontol*. 2006;77(8):1289-1303. doi:10.1902/jop.2006.050459
- 23. Preshaw PM, Alba AL, Herrera D, et al. Periodontitis and diabetes: a two-way relationship. *Diabetologia*. 2012;55(1):21-31. doi:10.1007/s00125-011-2342-y
- 24. Di Domenico GL, Minoli M, Discepoli N, Ambrosi A, de Sanctis M. Effectiveness of periodontal treatment to improve glycemic control: an umbrella review. *Acta Diabetol.* 2022;60(1):101-113. doi:10.1007/s00592-022-01991-z

- 25. Lavigne SE, Forrest JL. An umbrella review of systematic reviews examining the relationship between type 2 diabetes and periodontitis: Position paper from the Canadian Dental Hygienists Association. *Canadian journal of dental hygiene*. 2021;55(1):57–67.
- 26. Cullinan MP, Seymour GJ. Periodontal disease and systemic illness: will the evidence ever be enough? *Periodontol* 2000. 2013;62(1):271-286. doi:10.1111/prd.12007
- 27. Mehriz BM, Atteya MA, Skipina TM, Mostafa MA, Soliman EZ. Association between Periodontitis and Diabetes Mellitus in the General Population. *J Diabetes Metab Disord*. 2022;21(2):1249-1254. doi:10.1007/s40200-022-01010-6
- 28. Grossi SG, Genco RJ. Periodontal Disease and Diabetes Mellitus: A Two Way Relationship. *Ann Periodontol.* 1998;3(1):51-61. doi:10.1902/annals.1998.3.1.51
- 29. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an Umbrella review approach. *Int J Evid Based Healthc.* 2015;13(3):132-140. doi:10.1097/XEB.000000000000055
- 31. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. Published online March 29, 2021:n160. doi:10.1136/bmj.n160
- 32. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Published online March 29, 2021:n71. doi:10.1136/bmj.n71
- 33. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. Published online September 21, 2017:j4008. doi:10.1136/bmj.j4008
- 34. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. JAMA Surg. 2021;156(8):787. doi:10.1001/jamasurg.2021.0522
- 35. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int.* 2018;121(January):1027-1031. doi:10.1016/j.envint.2018.07.015
- 36. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. doi:10.1186/s13643-016-0384-4
- 37. Higgins J, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. version 6. Cochrane; 2023.
- 38. Pollock M, Fernandes RM, Becker LA, Pieper D, Hartling L. Chapter V: Overviews of Reviews. In: Higgins J, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.4. Cochhrane, 2023.
- 39. Hennessy EA, Johnson BT. Examining overlap of included studies in meta reviews: Guidance for using the corrected covered area index. Res Synth Methods. 2020;11(1):134-145. doi:10.1002/jrsm.1390
- 40. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: practical considerations for authors of overviews of reviews. *BMC Med Res Methodol.* 2021;21(1):140. doi:10.1186/s12874-021-01269-v
- 41. Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. *Commun Stat Theory Methods*. 2017;46(14):6774-6781. doi:10.1080/03610926.2015.1134575
- 42. Chen H, Cohen P, Chen S. How Big is a Big Odds Ratio? Interpreting the Magnitudes of Odds Ratios in Epidemiological Studies. *Commun Stat Simul Comput*. 2010;39(4):860-864. doi:10.1080/03610911003650383
- 43. Ryan R. Heterogeneity and subgroup analyses in Cochrane Consumers and Communication Group reviews: planning the analysis at protocol stage. *Cochrane Consumers and Communication Review Group*, 2013;2016(May):2-9.
- 44. Sälzer S, Slot DE, Van der Weijden FA, Dörfer CE. Efficacy of inter-dental mechanical plaque control in managing gingivitis a meta-review. *J Clin Periodontol*. 2015;42(S16):S92-S105. doi:10.1111/jcpe.12363
- 45. Hidding JT, Beurskens CHG, van der Wees PJ, van Laarhoven HWM, Nijhuis-van der Sanden MWG. Treatment Related Impairments in Arm and Shoulder in Patients with Breast Cancer: A Systematic Review. Macleod U, ed. *PLoS One*. 2014;9(5):e96748. doi:10.1371/journal.pone.0096748
- 46. Van der Weijden FA, Van der Sluijs E, Ciancio SG, Slot DE. Can Chemical Mouthwash Agents Achieve Plaque/ Gingivitis Control? Dent Clin North Am. 2015;59(4):799-829. doi:10.1016/j.cden.2015.06.002
- 47. Hill, AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58(5):295-300.
- 48. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD
- 49. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: A new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*. 2011;64(4):380-382. doi:10.1016/j.jclinepi.2010.09.011
- 50. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. Updated October 2013. Accessed December 12, 2023. https://gdt.gradepro.org/app/handbook/handbook.html
- 51. Idostatistics. Cohen's kappa calculator. NR. Accessed December 12, 2023. https://idostatistics.com/cohen-kappa-free-calculator/#risultati
- Larvin H, Kang J, Aggarwal VR, Pavitt S, Wu J. Periodontitis and risk of immune mediated systemic conditions: A systematic review and meta analysis. Community Dent Oral Epidemiol. 2023;51(5):705-717. doi:10.1111/cdoe.12812

- 53. Stöhr J, Barbaresko J, Neuenschwander M, Schlesinger S. Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Sci Rep.* 2021;11(1):13686. doi:10.1038/s41598-021-93062-6
- 54. Wu C zhou, Yuan YH, Liu HH, et al. Epidemiologic relationship between periodontitis and type 2 diabetes mellitus. *BMC Oral Health*. 2020;20(1):204. doi:10.1186/s12903-020-01180-w
- 55. Ziukaite L, Slot DE, Van der Weijden FA. Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies. *J Clin Periodontol.* 2018;45(6):650-662. doi:10.1111/jcpe.12839
- 56. Barutta F, Bellini S, Durazzo M, Gruden G. Novel Insight into the Mechanisms of the Bidirectional Relationship between Diabetes and Periodontitis. *Biomedicines*. 2022;10(1):178. doi:10.3390/biomedicines10010178
- 57. Borgnakke WS, Ylöstalo P V., Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *J Periodontol.* 2013;84(4-s):S135-S152. doi:10.1902/jop.2013.1340013
- 58. Graziani F, Gennai S, Solini A, Petrini M. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes An update of the EFP-AAP review. *J Clin Periodontol.* 2018;45(2):167-187. doi:10.1111/jcpe.12837
- 59. Borgnakke WS. "Non-modifiable" Risk Factors for Periodontitis and Diabetes. *Curr Oral Health Rep.* 2016;3(3):270-281. doi:10.1007/s40496-016-0098-7
- 60. Botero J, Rodríguez C, Agudelo Suarez A. Periodontal treatment and glycaemic control in patients with diabetes and periodontitis: an umbrella review. *Aust Dent J.* 2016;61(2):134-148. doi:10.1111/adj.12413
- 61. Otomo-Corgel J, Pucher JJ, Rethman MP, Reynolds MA. State of the Science: Chronic Periodontitis and Systemic Health. *Journal of Evidence Based Dental Practice*. 2012;12(3):20-28. doi:10.1016/S1532-3382(12)70006-4
- 62. Ioannidou E. The Sex and Gender Intersection in Chronic Periodontitis. Front Public Health. 2017;5. doi:10.3389/fpubh.2017.00189
- 63. Liu Y, Yu Y, Nickel JC, et al. Gender differences in the association of periodontitis and type 2 diabetes. *Int Dent J.* 2018;68(6):433-440. doi:10.1111/idj.12399
- 64. Kabisch S, Hedemann OS, Pfeiffer AFH. Periodontitis, age-related diseases and diabetes in an endocrinological outpatient setting (PARADIES): a cross-sectional analysis on predictive factors for periodontitis in a German outpatient facility. Acta Diabetol. 2022;59(5):675-686. doi:10.1007/s00592-021-01838-z
- 65. Boyapati R, Cherukuri S, Bodduru R, Kiranmaye A. Influence of female sex hormones in different stages of women on periodontium. *J Midlife Health*. 2021;12(4):263. doi:10.4103/jmh.jmh_142_21
- 66. López R, Smith PC, Göstemeyer G, Schwendicke F. Ageing, dental caries and periodontal diseases. J Clin Periodontol. 2017;44(S18):S145-S152. doi:10.1111/jcpe.12683
- 67. Clark D, Kotronia E, Ramsay SE. Frailty, aging, and periodontal disease: Basic biologic considerations. *Periodontol* 2000. 2021;87(1):143–156. doi:10.1111/prd.12380
- 68. Jepsen S, Caton JG, Albandar JM, et al. Periodontal manifestations of systemic diseases and developmental and acquired conditions: Consensus report of workgroup 3 of the 2017 World Workshop on the Classification of Periodontal and Peri Implant Diseases and Conditions. *J Periodontol.* 2018;89(S1):S237-S248. doi:10.1002/JPER.17-0733
- 69. Corbet EF, Leung WK. Epidemiology of periodontitis in the Asia and Oceania regions. *Periodontol 2000*. 2011;56(1):25-64. doi:10.1111/j.1600-0757.2010.00362.x
- 70. Huxley R, James WPT, Barzi F, et al. Ethnic comparisons of the cross sectional relationships between measures of body size with diabetes and hypertension. *Obesity Reviews*. 2008;9(s1):53-61. doi:10.1111/j.1467-789X.2007.00439.x
- 71. Chan JCN, Malik V, Jia W, et al. Diabetes in Asia. JAMA. 2009;301(20):2129. doi:10.1001/jama.2009.726
- 72. Ziukaite L, Slot DE, Coucke W, van der Weijden GA. Prevalence of diabetes among patients diagnosed with periodontitis: A retrospective cross-sectional study. *Int J Dent Hyg.* 2017;16(2):305-311.
- 73. Rosenthal JA. Qualitative Descriptors of Strength of Association and Effect Size. *J Soc Serv Res.* 1996;21(4):37-59. doi:10.1300/J079v21n04 02
- 74. Lovakov A, Agadullina ER. Empirically derived guidelines for effect size interpretation in social psychology. *Eur J Soc Psychol.* 2021;51(3):485–504. doi:10.1002/ejsp.2752
- 75. Demmer RT, Jacobs DR, Desvarieux M. Periodontal Disease and Incident Type 2 Diabetes. *Diabetes Care*. 2008;31(7):1373-1379. doi:10.2337/dc08-0026
- 76. Ide R, Hoshuyama T, Wilson D, Takahashi K, Higashi T. Periodontal Disease and Incident Diabetes. *J Dent Res.* 2011;90(1):41-46. doi:10.1177/0022034510381902
- 77. Morita I, Inagaki K, Nakamura F, et al. Relationship between Periodontal Status and Levels of Glycated Hemoglobin. *J Dent Res.* 2012;91(2):161-166. doi:10.1177/0022034511431583
- 78. Miyawaki A, Toyokawa S, Inoue K, Miyoshi Y, Kobayashi Y. Self-Reported Periodontitis and Incident Type 2 Diabetes among Male Workers from a 5-Year Follow-Up to MY Health Up Study. Kokubo Y, ed. *PLoS One*. 2016;11(4):e0153464. doi:10.1371/journal.pone.0153464
- 79. Kebede TG, Pink C, Rathmann W, et al. Does periodontitis affect diabetes incidence and haemoglobin A1c change?

- An 11-year follow-up study. *Diabetes Metab.* 2018;44(3):243-249. doi:10.1016/j.diabet.2017.11.003
- 80. Myllymäki V, Saxlin T, Knuuttila M, et al. Association between periodontal condition and the development of type 2 diabetes mellitus—Results from a 15 year follow up study. *J Clin Periodontol*. 2018;45(11):1276-1286. doi:10.1111/jcpe.13005
- 81. Winning L, Patterson CC, Neville CE, Kee F, Linden GJ. Periodontitis and incident type 2 diabetes: a prospective cohort study. *J Clin Periodontol*. 2017;44(3):266–274. doi:10.1111/jcpe.12691
- 82. Rezigalla AA. Observational Study Designs: Synopsis for Selecting an Appropriate Study Design. *Cureus*. Published online January 17, 2020. doi:10.7759/cureus.6692

"Een goed begin is het halve werk, maar een goed begin is maar de helft"

De Jeugd van Tegenwoordig

CHAPTER FOUR

What is the clinical periodontal condition of patients with diabetes mellitus as compared to those without?

A synthesis of systematic reviews

L.P.M. Weijdijk, G.A. Van der Weijden, S. Asadi, D.E. Slot *International Journal of Dental Hygiene (submitted)*



ABSTRACT

Focused question

What is the clinical periodontal condition of patients with diabetes mellitus (DM) as compared to those without DM (non-DM) as gathered from existing systematic reviews (SRs)?

Methods

MEDLINE-PubMed and the Cochrane Library were searched from inception through September 2024 to identify eligible studies. SRs evaluating the periodontal condition of periodontitis patients with DM versus non-DM were included. The primary outcome parameters of interest were Clinical Attachment level/loss (CAL) and Probing Pocket Depth (PPD). The secondary outcome were parameters of gingival inflammation, plaque and gingival recession. Characteristics, data and conclusions as presented in the selected SRs were extracted. The potential risk of bias was estimated, and a citation analysis was performed. The emerging evidence was summarized and grated.

Results

The search resulted in 488 unique titles and abstracts. After full text reading seven SRs were eligible for inclusion involving all together 154 underlying clinical studies. Of these 79 studies involved DM type I, 50 DM type II, 23 both types of DM and 2 studies without specification. For CAL the magnitude of the difference was estimated to be small to substantial for DM I and substantial for DM II and I/II. For PPD, the differences were estimated to be zero to moderate for DM I, moderate to substantial for DM II, and small to substantial for DM I/II.

Conclusion

Regarding the impact of DM on periodontitis parameters, there is a moderate certainty for a small to substantial difference on CAL and zero to substantial difference for PPD as compared to non-DM. There is weak evidence regarding the secondary parameters.

INTRODUCTION

Diabetes mellitus (DM) is a common chronic condition characterized by hyperglycemia resulting from an insulin deficiency or resistance. DM type I is an autoimmune disorder that primarily affects the peripheral system and is characterized by a chronic anti-self-inflammatory response. In contrast, DM type II is attributed to defects or alterations in the insulin molecule or the insulin receptor, resulting in insulin resistance. In 2019, the global prevalence of DM I and II was estimated at 9.3%, projected to increase to 10.2% (578 million) in 2030 and 10.9% (700 million) in 2045.

The presence of DM as a chronic disease may contribute to many complications, such as periodontitis. This oral disease condition leads to chronic inflammation and degradation of tissues surrounding the teeth. It is mainly manifested by attachment loss of the periodontium, which progresses to alveolar bone loss, potentially resulting in loss of the tooth. Periodontal diseases affect a significant proportion of the global population, with a prevalence rate of 20-50%. The severity and progression are influenced by factors such as heredity, oral hygiene and systemic diseases. 10,11

Scientific evidence has pointed to a bidirectional relationship between periodontal disease and DM.^{12–14} Both diseases are chronic, inflammatory, and multifactorial with inflammation playing a central role in their pathogenesis.¹⁶ Hyperglycemia is the most commonly identified link between periodontitis and DM, with a higher risk for both the development and progression of periodontitis in poorly controlled DM patients.¹⁶ In addition, periodontitis is associated with a potential adverse effect on glycemic control in DM patients.^{17–21} DM is generally associated with an increased incidence and severity of periodontitis.^{1,14} However, despite the growing body of literature on the association between DM and periodontitis, ^{22–25} no strong evidence supports a clear causal relationship.²⁶ The evidence on the relationship remains elusive and mainly the practical implication is unclear. There appears to be a need for a comprehensive and critical appraisal of the available evidence concerning the association between DM and periodontitis. Therefore, the aim of this study was to prepare a synopsis of synthesis (meta-review) on the outcome of clinical characteristics of periodontitis in patients with DM as compared to those without DM (non-DM).

METHODS

A protocol was developed 'a priori' following initial discussion between the members of the research team. The preparation and presentation of this meta-review is in accordance with the Joanna Briggs Institute (JBI) methodological guideline, the Meta-analysis of Observational Studies (MOOSE) guideline, the PRISMA guideline, and the AMSTAR tool. This study is registered at the International Prospective Register of Systematic Reviews (PROSPERO) under registration CRD42024550567. The Institutional Review Board of the Academic Centre for Dentistry Amsterdam (ACTA-ETC) also approved the study under the following number: 2023-7560.

Focused question

A review question was formulated utilizing the population, exposure, comparison, outcomes, and study (PECOS) framework³¹ resulting in: What is the periodontal condition in periodontitis patients with DM as opposed to those without DM, based on information gathered from existing systematic reviews (SRs)?

Search strategy

The electronic databases, including MEDLINE-PubMed, and special collections of the Cochrane-CENTRAL were systematically and comprehensively queried up to September 2024 to search for appropriate papers. The search was designed by the reviewers (LPMW, SA and DES) to include all SRs that answered the focused question. Table 1 provides more details regarding the search approach employed. The reference lists of the included SRs were hand-searched for supplementary SRs and the PROSPERO databases was checked for ongoing reviews. No further grey literature was sought.

Table 1

Search terms used for PubMed-MEDLINE and Cochrane Library.

{[<exposure>] AND [<outcome>]}

<Exposure>

<(("Periodontitis" [Mesh]) OR Periodontitis OR (periodontal disease) OR (periodontal diseas*) OR (periodontal infection) OR periodont*)>

AND

<Outcome:>

 $<((``Glucose\ Metabolism\ Disorders''\ [Mesh])\ OR\ (``Diabetes\ Mellitus''[Mesh])\ OR\ (Diabetes\ Mellitus)\ OR\ Diabetes\ OR\ diabet*\ OR\ glucose\ metabolism\ disorders)>$

ANC.

<(systematic review* OR meta-analysis OR meta analysis OR umbrella review*)>

The asterisk (*) was used as a truncation symbol. The search strategy was customized according to the database being searched.

Screening and selection

Titles and abstracts of all studies identified through the searches were screened. This process was independently performed by two reviewers (LPMW and SA) using the Rayyan web application^{32,33} and categorized as included, excluded or undecided using the inclusion criteria. The reviewers were blinded from each other's results during the two-staged selection

process. After the screening process the search was unblinded and disagreements concerning eligibility were identified and discussed. Subsequently, the papers of the abstracts meeting the predefined criteria underwent a comprehensive evaluation by thoroughly examining the full text by two reviewers (LPMW and SA). Updates of SRs were checked, and the latest version was selected. Any disagreement between the two reviewers regarding study eligibility was resolved after additional discussion. If disagreement persisted, then a third reviewer (DES) was consulted, whose judgement was considered then to be decisive. The reasons for exclusion after full-text reading were recorded (see Online Appendix S1). The selected SRs that fulfilled the eligibility criteria were identified and included in this meta-review, then processed for data extraction and risk of bias estimation.

Inclusion and exclusion criteria

Studies were deemed eligible for inclusion if they conformed to the following criteria:

- SRs with a meta-analysis. Data from a SR were taken into consideration if more than one original study contributed to the underlying evidence.
- Full text publications available in English.
- SRs of studies conducted in humans that had at least two groups of individuals:
 - Evaluating patients with DM (or any other synonym, such as metabolic syndrome (MetS)).
 - Evaluating people without DM.
- Studies assessing periodontal disease related outcomes as confirmed by any of the following:
 - Primary outcomes: Probing Pocket Depth (PPD) and/or Clinical Attachment level/ loss (CAL).
 - If available, secondary outcomes: gingival inflammation (such as bleeding on probing (BOP) or gingival index (GI)), plaque scores and gingival recession (GR).

The exclusion criteria were as follows:

- Gestational DM (GDM) and prediabetes
- Apical periodontitis
- Peri-implantitis
- Periodontitis defined only by number of teeth or tooth loss
- Studies that primarily focus on dental implants
- Studies that primarily focused on the effect of periodontal treatment

Quality assessment

The quality assessment of the included SRs was performed independently and in duplicate by two reviewers (LPMW and DES) in accordance with the PRISMA guideline²⁹ and the AMSTAR checklist,^{30,34} for assessing the methodological quality of SRs. A list of 27 items was assessed, and an overall percentage score was obtained based on a summary of the scores of all individual items which were given a positive rating. The outcome was judged on the criteria as presented by Van der Weijden & Slot (2015).³⁵

Operationalization outcomes measure Primary outcome parameters

Primary outcomes were determined as follows:

- PPD: periodontal pocket depth as measured from the gingival margin to the base of the periodontal pockets with the tip of the periodontal probe and expressed in mm.³⁶
- CAL: clinical attachment level/loss as measured with a periodontal probe from the cement-enamel junction (CEJ), or Relative Attachment Level (RAL) using a customized stent to the base of the pocket, and both expressed in mm.

Secondary outcome parameters

The secondary outcomes were determined as follows:

- Gingival Index³⁷
- Gingival bleeding indices such as BOP and GBI,³⁸ PBI^{39,40} or SBI⁴⁰
- Plaque indices: Pl,⁴¹ VPl⁴² or APl⁴²
- Gingival recession: gingival recession as clinically measured from the CEJ to marginal gingiva^{43,44}

Data analysis

Assessment of heterogeneity

The heterogeneity across studies was detailed according to the following factors:

- Methodological: variability in review approach, risk of bias assessment and analysis performed (descriptive and/or meta-analysis).
- Clinical: subject characteristics, details on severity of periodontitis and details concerning DM diagnose (type I, type I/II or not-specified).

Citation analysis

To ascertain potential overlap among the primary clinical studies within the included SRs, a citation matrix was constructed. This matrix aimed to compile a comprehensive list of the underlying unique studies in the SRs.⁴⁵ For each of these studies the type of DM that was evaluated was recorded.

Data extraction

The papers that were included after the screening and selection were processed for data extraction. If studies examined a bi-directional relationship of periodontitis and DM only those data were extracted that evaluated DM as exposure variable and periodontitis as outcome. Data from SRs were extracted when a minimum of two original studies on the reported outcomes of interest had been included for the analysis. Independent data extraction was performed by two reviewers (LPMW and SA) using a standardized data extraction form. A third author (DES) confirmed the categorization. Any disagreements between the reviewers were solved by discussion.

The following characteristics of the included studies were extracted: publication details, focused question, search results, number of included studies, details on DM, periodontal outcomes and the conclusion from the original SR. The method of analysis, descriptive and/or involving meta-analysis was also documented. From the meta-analysis, difference of means (DiffM) also referred to as weighted mean difference (WMD) or standardized mean difference (SMD) and the corresponding standard deviations (SD), 95% confidence intervals

(CI) and p-values were extracted from both random- and fixed-effects models. Statistical heterogeneity was extracted such as, I² and/or Cochrane Q, with the respective p-values.

Data interpretation

Details regarding the interpretation of the outcomes are presented in Table 2.

As a guide for interpreting the clinical magnitude of the association of the primary clinical outcomes the guidelines as presented by Smiley et al. (2015)⁴⁶ was used and for secondary outcomes the outcomes as presented as SMD judged according to Cohen d. (1988).⁴⁷ Meta-analyses outcomes resulting in a p<0.05 were considered to be statistically significant. If the p-value was not given, the level of significance was interpreted based on the confidence interval. The I² statistic was used to quantify heterogeneity and calculate the proportion of variation due to heterogeneity rather than due to chance. Tests of statistical heterogeneity resulting in a p<0.1 were considered to be statistically significant. As a rough guide to interpret the % potential magnitude of inconsistency between studies the Cochrane Handbook section

Table 2Data interpretation

9.5.2 was followed.48

Significance(p) ¹		•	outcomes: p≥0.05 tcomes: p<0.05	
Meta-analysis outcome PPD/CAL Smiley et al. ²	Zero 0-0.2	Small 0.2-0.4	Moderate 0.4-0.6	Substantial >0.6
Meta-analysis outcome SMD ³	None 0-0.2	Small >0.2 - ≤0.5	Medium >0.5- ≤0.8	Large >0.8
Test of heterogeneity (I2)4	Potential not important 0–40%	Moderate 30-60%	Substantial 50–90%	Considerable 75–100%

 $^{{\}tt Meta-analyses\ outcomes\ resulting\ in\ a\ p<0.05\ was\ considered\ to\ be\ statistically\ significant}$

Grading the 'Body of Evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system⁴⁹, proposed by the GRADE working group, was used to assess the quality of evidence generated from this synopsis of SRs.⁵⁰⁻⁵² Two reviewers (LPMW and DES) graded the quality of the evidence and strength based on several factors such as study design, risk of bias, consistency and precision among outcomes, directness of the evidence, detection of publication bias and magnitude of the effect.

²As a guideline, the magnitude of 0-0.2 considered indicative zero effect, an effect size of 0.2-0.4 is a small effect, an effect size of 0.4-0.06 is a moderate effect size, and a >0.6 is a substantial effect for CAL.

³As a guideline, the magnitude of 0-0.2 considered indicative no effect, an SMD of 0.2-0.5 is a small effect, an SMD of 0.5-0.8 is a medium effect size, and a >0.8 is a large effect for SMD.

⁴As a guideline, to assess the potential magnitude of inconsistency between studies, an I² statistic of 0%-40% may represent unimportant levels of heterogeneity, 30%-60% may represent moderate heterogeneity, 50%-90% may represent substantial heterogeneity. An I² statistic of greater than 75% was interpreted to indicate considerable heterogeneity.

RESULTS

Search and selection results

Figure 1 illustrates the search and selection process. In short, a total of 488 unique articles were identified, 19 were read in detail and 12 were excluded (for details see Online Appendix S1), consequently, seven SRs were included. 14,21,53-57 An overview of the selected SRs, their characteristics and the identifiers used in this paper (I-VII) are presented in Table 3.

Figure 1



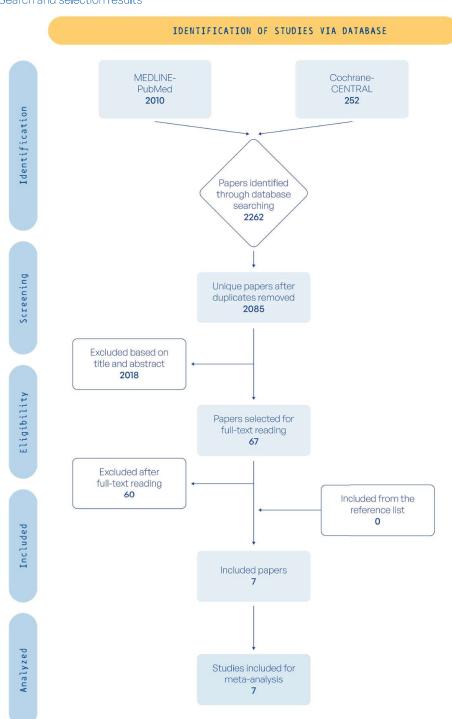


Table 3

Overview of the characteristics of the included SRs processed for data extraction.

Author, year, Rob	Databases Searched	No. Of included Studies, Trails/No. Involved Participants, DM and non-DM	Type of DM #studies	Used Periodontal parameters in the SRs	Original review authors conclusions	Comments of the meta-review authors
I: Zainal Abidin et al. 2021 Rob: moderate	EBSCO, Medline Complete, Pubmed, Science Direct, manual search (reference lists)	11 studies N=1625 () DM N=846 () Non-DM N=779 ()	DM I (824¢) DM II (10¢) DM unspecified (12)	CAL*, PPD BOP, bleeding on site, Gl, PI	Children and adolescents with DM have poorer periodontal status compared to their non-DM counterparts.	Only one clinical study was of good quality, while the remaining ten clinical studies were of fair quality. One clinical study did not specify the type of DM. Random-effect models were used in studies ≤3 clinical papers. Only children and adolescents were included (range 3-19y).
II: Jensen et al. 2021 Rob: moderate	Pubmed, EMBASE	23 studies N=3529 DM N=? Non-DM N=?	DM I (?)	CAL*, PPD BOP, GI, PI	Children and adolescents with DM I are more likely to have higher PI, GI, BOP, PD and CAL risk markers for periodontal disease compared to healthy control groups.	It is not clearly defined how many DM I patients and how many healthy controls were involved. Only children and adolescents were included (range 2-18y).
III: Wu et al. 2020 Rob: low	MEDLINE, EMBASE, Chinese BioMedical Literature Database, China National Knowledge Infrastructure, manual search (reference lists, Journals)	53 studies N=48142 () DM N=6210 () Non-DM N=27595 ()	DM II (62100)	CAL, PPD	There is a relationship between DM II and periodontitis.	The number of cohort studies is limited. The SR is mainly focused on how periodontitis influences DM II progression. It is unclear if children were included.
IV: Rapone et al. 2020 Rob: substantial	MEDLINE, manual search	10 studies N=1820 \$\text{DM}\$ DM N=941 \$\text{NDM}\$ NBM N=879 \$\text{SP}\$	DM1(941())	CAL, PPD, BOP, Gl, PI	There is no strong evidence that periodontitis is a significant risk factor for DMI, and the link between PD and DMI appears to be less established than the connection with DMII.	Only MEDLINE were used as database. The included clinical studies were mainly cross-sectional studies and often of low quality. Only children and adolescents were included.

V: Dicembrini et	V: Dicembrini et MEDLINE, Cochrane	19 studies	DMI(?)	CAL	DM I is a relevant risk factor for the	It is not clearly defined how many DM I
al. 2020	Central Register of	:=N			development of periodontal	patients and how many healthy controls
	Trials, EMBASE,				disease. Periodontal disease is more	were involved.
Rob: moderate	manual search	MO			than doubled in subjects with DM I	The studies that were included in the
	(reference list,	N=?			compared to non-DM individual.	SR were mainly cross-sectional studies.
	Journals)					Both children and adults were included.
		Non-DM				
VI. Obávorova	Duby London	[N=:	(0) 1740		DM II may be a rick for populatitie	Hio under defined bear month of
VI. Cildvali y et	rublyled, Ellipase,	o/ studies		OAL , 11D	DIVILLITIAY DE A LISA TOL PELLOGOLITIUS,	Icis unideal delined now many Divi
al. 2009	SOIELO, LILACS,		UMIII (:)		more studies are needed to confirm	patients and now many controls were
	manual search				the effects of DM I.	involved.
Rob: moderate		DM				Both children and adults were included.
		N=?				
		Non-DM				
		N=?				
VII: Khader et al.	MEDLINE, manual	23 studies	DMI (?)	CAL*, PPD	DM individuals had significantly	In three studies, the type of DM was not
2006	search (reference	N=19245()	DM II (?)	BOP, GI, PI,	higher severity, but the same extent	specified.
	lists)		DM I/II (?)	GR	of periodontal disease compared to	It is unclear defined how many DMI, II,
Rob: substantial		DM	DM unspecified		non-DM.	I/II patients were involved.
		N=1835	(2)			Subgroup analysis was not possible due
						to missing information in the included
		Non-DM				articles.
		N=17410				Both children and adults were included
						(5-78y).

Abbreviations: ? unknown, § calculated, CAL clinical attachment level, CAL* clinical attachment loss, PPD periodontal pocket depth, BOP bleeding on probing, G/ gingival index, P/ plaque index, GR gingival recession, DM diabetes mellitus, DM // diabetic mellitus, DM // diabetes mellitus, DM // di

Assessment of heterogeneity

The seven SRs analyzed in this synthesis showed heterogeneity with respect to the databases that were searched, characteristics of the original studies, the included subjects, inclusion and exclusion criteria, the quality assessment method employed, methods of recording and reporting, and their conclusions.

Assessment of citations

The citation matrix, presented in Online Appendix S2, provides a comprehensive list of the primary underlying studies identified in each of the SRs included in this synthesis. The seven SRs comprised in total 112 unique clinical studies. No SRs included all of these papers. The matrix shows that 81 papers appeared only once across the SRs, 22 papers were included in two SRs, 7 papers were included in three SRs, and 2 papers appeared in four SRs. Based on the inclusion by publication date, but irrespective of the selection criteria, potentially 90 to 154 papers could have been included in each SR. Effectively 7-46% of those that could potentially have been included were selected based on the eligibility criteria. There was also variation in the number of underlying included studies in the selected SRs concerning the type of DM. In total 79 studies evaluated the periodontal condition in DM I compared to those without DM, 50 in DM II and 23 papers in both DM type I and II. Two clinical studies within the included SRs did not explicitly specify the specific type of DM.

Quality and risk of bias assessment

Online Appendix S3 presents the risk of bias assessment for the seven included SRs. SR III were rated as having a low estimated risk of bias, while SR I, II, V and VI were considered as having a moderate risk of bias. SR IV and VII were found to exhibit a substantial risk of bias.

Data analysis

Details of the extracted data for the primary and secondary periodontal parameters are shown in Table 4. A majority of the included SRs showed significant differences for the clinical periodontal outcomes with non-DM showing lower values. Most meta-analyses, in the included SRs showed substantial (50-90%) to considerable statistical heterogeneity (75-100%).⁴⁸ A total of 11 comparisons of seven SRs were available: six comparisons of DM I, three comparisons of DM II and two comparisons of both DM I/II.

Primary outcome parameters

All seven SRs (I-VII) reported statistically significant differences for their meta-analyses on CAL $_{\rm evel}$ (III, IV, V) and CAL $_{\rm oss}$ (I,II, VI, VII) between DM patients compared to non-DM patients with higher scores for those with DM. A total of 3 comparisons indicated significant differences for CAL $_{\rm evel}$: in 2/2 for DM I and 1/1 for DM II. For CAL $_{\rm oss}$ 7 comparisons could be made: in 3/3 for DM I, 2/2 for DM II and 2/2 for DM I/II. For details see Table 4.

The magnitude of the difference was estimated regarding CAL_{oss} to be small to moderate for DM I (ranging from 0.26-0.652) and substantial for DM II (0.691-1.00) and DM I/II (0.612-0.78). For CAL_{evel} the magnitude was moderate to substantial (0.468-0.82) for DM I and substantial for DM II (0.89). (Table 5A+C). The heterogeneity of the meta-analysis was estimated to range from potentially substantial to considerable.⁵⁸

Among the seven SRs that examined PPD measurements, six SRs (I-V, VII) found significant differences between DM and non-DM patients, while one SR (VI) did not (p=0.137). Corresponding with a value of 3/4 for DM I, 3/3 for DM II and 2/2 for DM I/II, see Table 4. The

magnitude of the difference in PPD was estimated to be zero to moderate for DM I (0.11-0.55), moderate to substantial for DM II (0.46-0.61) and small to substantial for DM I/II (0.346-0.67) (Table 5A+C). The heterogeneity of the meta-analysis ranged from potentially not important to considerable.⁵⁸

Secondary outcome parameters

For BOP four SRs (I, II, IV, VII) provided data and six comparisons were available; 4/4 showed significant differences for DM I, 0/1 for DM II and 0/1 for DM I/II compared to non-DM (Table 4). For three SRs (I, II, IV) focusing on DM I the meta-analysis provide an SMD for which the difference was interpreted as a small to medium (0.32-0.65), 47 see Table 5B+C. The heterogeneity of the meta-analysis is estimated to range from potentially not important to substantial. 58

For the GI four SRs (I, II, IV, VII) provided data within six comparisons. For DM I and DM I/II all outcomes were significant, 3/3 and 2/2 respectively. For DM II one comparison could be included from SR VII showing no significant difference (p=0.2628), see Table 4. For the SRs that presented a SMD the magnitude of the difference could be interpreted as small to medium (0.46-0.51) for DM I and medium for DM II (0.63).⁴⁷ All meta-analysis in the SRs had considerable heterogeneity, except for SR VII.⁵⁸ For details see Table 5B+C.

Four of the seven SRs reported outcomes on plaque (I, II, IV, VII). All outcomes were statistically significant between DM and non-DM, except for SR VII (p=0.0819) on DM II. A total of six comparisons could be extracted, indicating higher scores for DM I 3/3 and DM I/II 2/2, for DM II no significant outcomes were found (0/1) (Table 4). The magnitude of the difference was estimated as small to medium for DM I (0.45-0.71) and small for DM I/II (0.54), see Table 5B+C. The majority of the SRs reported significant heterogeneity in the meta-analysis. For GR one comparison could be included based on one SR (VII) focusing on DM I/II, however no significant difference was found (p=0.4835). Heterogeneity of the meta-analysis was not significant. See Table 5B.

Table 4

A table of statistical significance levels of the difference between types of DM patients compared to non-DM regarding to primary and secondary parameters.

	_		Primary			Secor	ndary		
Author	Exposure	CA	AL	PPD	PI	ВОР	GI	GR	Comparison
		CALevel	CALoss						
l: Zainal Abidin et al. 2021	DMT					+			non-DM
II: Jensen et al. 2021	DMT		+	+	+	+	+		non-DM
IV: Rapone et al. 2020	DMT	+		+	+	+	+		non-DM
V: Dicembrini et al. 2020	DMT	+							non-DM
VI: Chávarry et al. 2009	DMT		+	0					non-DM
VII: Khader et al. 2006	DMT		+	+	+	+	+		non-DM
Sub-analysis DM I		2/2 100%	3/3 100%	3/4 75%	3/3 100%	4/4 100%	3/3 100%		
III: Wu et al. 2020	DM II	+		+					non-DM
VI: Chávarry et al. 2009	DMII		+	+					non-DM
VII: Khader et al. 2006	DMII		+	+	0	0	0		non-DM
Sub-analysis DM II		1/1 100%	2/2 100%	3/3 100%	0/1 0%	0/1 0%	0/1 0%		
l: Zainal Abidin et al. 2021	DM I/II		+	+	+		+		non-DM
VII: Khader et al. 2006	DM I/II		+	+	+	0	+	0	non-DM
Sub-analysis DM I/II		0/0 0%	2/2 100%	2/2 100%	2/2 100%	0/1 0%	2/2 100%	0/1 0%	
Overall		4/4	7/7 100%	9/10 90%	6/7 86%	5/7 71%	6/7 86%	0/1	

(grey) no data available, + (green) DM group significant more severe than non-DM, 0 (orange) no difference between DM group and non-DM. Abbreviations: DM I diabetes mellitus type I, DM II diabetes mellitus type II, DM II diabetes mellitus type I or II or both, DM type unspecified, non-DM: no diabetes mellitus, CAL clinical attachment level, PPD periodontal pocket depth, BOP bleeding on probing, GI gingival index, PI plaque index, GR gingival recession.

Table 5A

Overview of data extraction of the included SRs regarding primary outcomes. See Table 2 for interpretation

	Source		0	Outcome		Heterogeneity	eneity
Periodontal parameters	SRs	No. studies included in meta-analysis	Effect model (random/fixed): Difference of Means/SMD*/WMD**	IO %656	<u>a</u>	12/Q*	ä
CALoss	I: Zainal Abidin et al. 2021	3 (DM I/II	Random: 0.79*	0.52;1.05	<0.00001	77	0.03
	II: Jensen et al. 2021	7 (DMI)	Random: 0.54*	0.29;0.78	<0.0001	75	0.0005
	VI: Chávarry et al. 2009	9 (DMI)	Random: 0.26	-0.004;0.533	0.054	11.526***	0.17
		3 (DM II)	Random: 1.00	0.15;1.84	0.021	2.416***	0.2990
	VII: Khader et al. 2006	8 (DM I/II)	Random: 0.612	0.462;0.761	<0.0001		<0.0001
		6 (DMI)	Random: 0.652	0.465;0.840	<0.0001		<0.0001
		4 (DM II)	Random: 0.691	0.427;0.956	<0.0001		<0.0001
CALevel	III: Wu et al. 2020	18 (DM II)	Random: 0.89**	0.64;1.15	0.000	92.5	0.000
	IV: Rapone et al. 2020	4 (DM I)	Random: 0.82*	0.59;1.04	<0.0001	58.5	0.0648
	V: Dicembrini et al. 2020	10 (DMI)	Random: 0.492**	0.198;0.786	0	85.9	<0.005
			Random: 0.468*	0.368;0.568	0.000		
		HbA1c >7%	Random: 0.71	-1.000;-0.421	0.000	89.8	<0.001
PPD	I: Zainal Abidin et al. 2021	4 (DM I/II)	Random: 0.67*	0.23;1.11	0.003	75	0.003
	II: Jensen et al. 2021	8 (DMI)	Random: 0.55*	0.22;0.87	0.001	73	0.0005
	IV: Wu et al. 2020	17 (DM II)	Random: 0.61**	0.42;0.79	0.000	94.5	0.000
	IV: Rapone et al. 2020	2 (DMI)	Random: 0.36*	0.16;0.55	<0.001	0	0.4
	VI: Chávarry et al. 2009	10 (DM I)	Random: 0.11	-0.03;0.245	0.137	.220***	0.614
		5 (DMII)	Random: 0.46	0.01;0.91	0.046	5.147***	0.273
	VII: Khader et al. 2006	7 (DMI/II)	Random: 0.346	0.194;0.498	<0.0001	0	<0.0001
		6 (DMI)	Random: 0.280	0.115;0.445	0.0001		<0.0001
		3 (DMII)	Random: 0.546	0.299;0.793	0.0002	11	<0.0001

Abbreviations: [] no data available, CAL clinical attachment level, PPD periodontal pocket depth, DM / diabetes mellitus type I, DM // diabetes mellitus type II, DM // diabetes mellitus type II, DM // diabetes mellitus type I or II or both, DM type unspecified, *DiffM difference of means, *SMD standardized mean difference, **WMD weighted mean difference, ***calculated as Cochran's Q.

Table 5B

Overview of data extraction of the included SRs regarding primary outcomes. See Table 2 for interpretation

	Source		nO	Outcomes		Heterogeneity	eneity
	SRs	No. studies	Effect model	IO %56	۵	l ² /Q*	Pa
Periodontal		included in meta-	(random/fixed):				
		alialysis	Means/SMD*/WMD**				
BOP	I: Zainal Abidin et al. 2021	3 (DMI)	Random: 0.32*	0.07;0.58	0.01	0	96:0
	II: Jensen et al. 2021	12 (DM I)	Random: 0.61*	0.40;0.82	<0.00001	80	<0.0001
	IV: Rapone et al. 2020	3 (DMI)	Random: 0.65*	0.08;1.23	0.024	80.9	0.0053
	VII: Khader et al. 2006	5 (DMI/II)	Random: 0.157	-0.034;0.347	0.1068		NS
		3 (DMI)	Random: 0.424	0.189;0.659	0.0004		NS
		3 (DM II)	Random: 0.150	-0.054;0.354	0.1450		SN
Ō	I: Zainal Abidin et al. 2021	10 (DM1/II)	Random: 0.63*	0.39;0.87	<0.00001	77	<0.00001
	II: Jensen et al. 2021	18 (DM I)	Random: 0.51*	0.28;0.74	<0.0001	98	<0.00001
	IV: Rapone et al. 2020	7 (DMI)	Random: 0.46*	0.08;0.84	0.016	90.1	<0.0001
	VII: Khader et al. 2006	8 (DM I/II)	Random: 0.147	0.012;0.281	0.0331		NS
		7 (DMI)	Random: 0.652	0.465;0.840	<0.0001		NS
		2 (DM I/II)	Random: 0.149	-0.112;0.411	0.2628		NS
Ы	I: Zainal Abidin et al. 2021	11 (DM I/II)	Random: 0.54*	0.20;0.87	0.002	88	<0.00001
	II: Jensen et al. 2021	20 (DMI)	Random: 0.45*	0.21;0.70	0.0003	90	<0.00001
	IV: Rapone et al. 2020	7 (DMI)	Random: 0.71*	0.19;1.22	0.007	93.5	<0.0001
	VII: Khader et al. 2006	10 (DM I/II)	Random: 0.218	0.098;0.337	0.0003		<0.0001
		8 (DMI)	Random: 0.220	0.082;0.357	0.0017		<0.0001
		3 (DM II)	Random: 0.191	-0.024;0.406	0.0819		NS
GR	VII: Khader et al. 2006	2 (DM I/II)	Random: 0.086	-0.155;0.327	0.4835		<0.0001

Abbreviations: [] no data available, BOP bleeding on probing, G/gingival index, P/P plaque index, GR gingival recession. DM // diabetes mellitus type II, DM // diabetes mellitus type II, DM // diabetes mellitus type II or II or both, DM type unspecified, NS not significant, *DiffM difference of means, *SMD standardized mean difference, ***WMD weighted mean difference, ****calculated as Cochran's Q.

Table 5C

Interpretation of the magnitude of the difference regarding the primary and secondary outcomes. See Table 2+3 for interpretation

Periodontal parameter	DM type	Range	Interpretation
Primary outcomes			
CALevel	DMT	0.468-0.82	Moderate to substantial
	DMII	0.89	Substantial
	DM I/II	NA	NA
CALoss	DMT	0.26-0.652	Small to moderate
	DMII	0.691-1.00	Substantial
	DM I/II	0.612-0.78	Substantial
PPD	DMT	0.11-0.55	Zero to moderate
	DMII	0.46-0.61	Moderate to substantial
	DM I/II	0.346-0.67	Small to substantial
Secondary outcomes			
ВОР	DMT	0.32-0.65	Small to medium
	DMII	NA	NA
	DM I/II	NA	NA
GI	DMT	0.46-0.51	Small to medium
	DMII	0.63	Medium
	DM I/II	NA	NA
Pl	DMT	0.45-0.71	Small to medium
	DMII	NA	NA
	DM I/II	0.54	Small
GR	DM I/II	NA	NA

Abbreviations: DM / diabetes mellitus type I, DM // diabetes mellitus type II, DM // diabetes mellitus type I or II or both, DM type unspecified, CAL clinical attachment level, PPD periodontal pocket depth, BOP bleeding on probing, G/ gingival index, P/ plaque index, GR gingival recession

Evidence profile

Table 6 depicts a comprehensive summary of the various aspects that were used to rate the quality and strength of the evidence according to the GRADE working group. ^{49,50} The estimated risk of bias in the included SRs varied from low to substantial. Publication bias was considered to be possible. With respect to the impact of DM and parameters of periodontitis there was a moderate certainty for a small to substantial difference on CAL and zero to substantial for PPD as compared to non-DM. There was weak evidence regarding the secondary parameters.

Table 6Estimated evidence profile for primary and secondary outcome parameters.

GRADE	Primary parameters		Secondary parameters
	CAL(loss/level)	PPD	BOP/GI/PI/GR
Study designs	SRs	SRs	SRs
#	n=7	n=6	n=4
Reporting and	Low to substantial	Low to substantial	Low to substantial
methodological			
estimated potential			
risk of bias			
Consistency	Rather consistent	Rather consistent	Rather consistent
Directness	Rather generalizable	Rather generalizable	Rather generalizable
Precision	Precise	Precise	Rather imprecise
Publication bias	Possible	Possible	Possible
Magnitude of the	Small to substantial	Zero to substantial	Unclear
effect			
Body of evidence	Moderate strength	Moderate strength	Weak strength
Summary and	Regarding the impact of	of DM on periodontitis para	meters, there is a moderate
direction of the	certainty for a small to	substantial difference on (CAL and zero to substantial
findings	difference for PPD as c	ompared to non-DM. There	e is weak evidence regarding
	the secondary paramet	ers.	

Abbreviations: CAL clinical attachment level, PPD periodontal pocket depth, BOP bleeding on probing, GI gingival index, PI plaque index, GR gingival recession

DISCUSSION

Summary of key findings

This synthesis aimed to summarize the evidence from existing SRs concerning the relationship between DM and periodontal outcomes in patients with periodontitis. Specifically, SRs were chosen as primary source of evidence since they generally provide more comprehensive evidence than individual observational studies alone. Analysis of the eight SRs included in this synthesis demonstrated higher and significant values of the primary periodontal parameters in patients with DM compared to non-DM. The magnitude of the difference was estimated to be small to substantial concerning CAL and zero to substantial for PPD. The findings should be interpreted with caution considering the heterogeneity, limitations and potential biases in the data that emerged from the included SRs and their underlying studies.

The association between DM and periodontitis

Numerous studies have been conducted to investigate the bi-directional relationship between DM and the periodontal condition. 22-25 17,24,60,61 It has been suggested that DM leads to worsening of periodontal disease, which is more prevalent and severe compared to non-DM. Mechanisms that link these two conditions involve aspects of inflammation, immune functioning, neutrophil activity and cytokine biology.62 These factors collectively contribute to the development and progression of both conditions. This synopsis shows that the overall findings from multiple clinical studies potentially suggest an influence of DM on periodontal outcomes. However, based on the available data a causal relationship could not be established. The presence of an association and possible causal relationship is widely promoted by the European Federation of Periodontology (EFP). In collaboration with the International Diabetes Federation (IDF) a consensus guideline has been made. 63 This guideline offers recommendations to physicians, oral health care professionals and patients to improve early diagnosis, prevention and comanagement of DM and periodontitis. It suggests integrating oral health education into DM care, educating patients about the risks and complications of untreated periodontitis, and encouraging regular periodontal check-ups and referrals to dental professionals as part of DM management. The direction of the guideline was based on statistically significant differences obtained in majority of individual studies and SRs. In order to determine the clinical relevance interpretation of these differences between DM and non-DM there is need to evaluate not only the association between DM and periodontitis but also the strength of the association as a measurement of the overall effect.64

DM type I and II

When interpreting the differences, the magnitude of the primary outcomes generally ranged from small to substantial for CAL and zero to substantial for PPD (Table 5C). However, when only DM I was considered, a small to substantial effect was found for CAL, and a zero to moderate effect for PPD. In studies involving patients with type II DM, more pronounced differences were noted, with both parameters showing a moderate to substantial effect. This is consistent with the finding of a substantial effect when both types (DM I and II) were analyzed together, supporting the findings that type II DM likely has a greater impact on the periodontal condition compared to DM type I. This could be explained by the fact that the age of the studies involving DM type I especially include people \leq 18 years, which is considerably younger than the age range in which DM II develops. It is not common for individuals at this young age group to develop severe periodontal disease. According to the Global Burden of Periodontal disease study the highest incidence for periodontitis is found around the

age of 38.⁶⁷ This is approximately the same age that patients start to develop type II DM.⁶⁷⁻⁶⁹ Moreover, DM type II is often associated with a longer duration of hyperglycemia,⁵ which may allow more time for inflammatory mechanisms to become established potentially contributing to the development of periodontal disease. Additionally, the presence of insulin resistance and other comorbid conditions, such as obesity and cardiovascular disease, may exacerbate the inflammatory response and negatively impact periodontal health,⁷⁰⁻⁷² resulting in a more pronounced effects for type II DM. It is important to note that in some of the SRs included in this meta-review, there was a lack of clarity regarding the type of DM involved. Some SRs included individuals without clear distinction between DM I and II. This may have implications for the interpretation and generalizability of the results.

Risk factors

The condition known as prediabetes is characterized as the phase preceding established DM, during which blood glucose levels are elevated beyond the normal range but below the threshold defined for individuals with DM.⁷³ Prediabetes is reversible by improving lifestyle factors although it possesses risk factors for the development of DM II.⁷⁴ For this reason, prediabetes has been excluded from this meta-review. Another risk factor for developing DM II is GDM.⁷⁵ This is primarily a pregnancy-related condition that arises from hormonal changes affecting insulin sensitivity during pregnancy⁷⁶ and was consequently not analyzed in the present meta-review. A well-known risk factor for both DM and periodontal disease is smoking.^{77,78} Smoking is an independent risk factor for the initiation, extent and severity of periodontal disease.⁷⁹ In addition, periodontal disease is found to be more advanced in smokers with DM diabetic smokers compared to non-DM smokers.⁸⁰ Another risk factor is gender. Higher prevalence rates of moderate-severe periodontitis existed in diabetic, older and male individuals.⁸¹ However, analysis on gender and smoking could not be performed as the original SRs did not perform subgroup analysis according to these factors.

Parameters for periodontal condition

The extent and severity of periodontitis can be assessed using various parameters. In this meta-review CAL, PPD, GR, gingivitis and plaque indices were used. Tooth loss is often mentioned as the ultimate outcome and endpoint parameter for periodontitis. B2,83 In the present review tooth loss was not included as it can also be attributed to other pathological conditions such as dental caries. However, a recent SR presenting a small but significant higher risk (RR=1.63, p<0.00001) for tooth loss in patients with DM. However, tooth loss represents the final outcome of disease progression, rather than an indicator of its current activity. Loss of periodontal tissue attachment due to inflammation is the primary feature of periodontitis. Parameters like CAL, PPD and GR directly assess the clinical and structural changes occurring in the periodontium, providing a surrogate parameter of the periodontal tissue loss as a result of the inflammatory process.

Interpretation and methodological approach

The primary outcomes are interpreted based on the criteria presented by Smiley et al. ⁴⁶ Although this guideline is specifically intended for the interpretation changes in CAL, it was for this metareview also applied to assess the magnitude of effect on PPD. Increase in the PPD is dependent on attachment loss but also influenced by the change (recession) in the level of the marginal gingiva. Considering that both these aspects may play a role in the observed PPD the size of the difference in PPD should at least be as large as CAL when no recession occurs. In case of this meta-review no significant difference in the level of recession was observed (see SRVII, table 5B).³⁶

A point estimate is an estimation for an average estimated effect size. The 95%CI that goes along with it is the variation around this point estimate. In general, the smaller the 95%CI, the more precise the estimate of the effect size. Together, the point estimate and the 95%CI provide information to assess the clinical relevance of the data. Especially SR VII 21 found relatively narrow 95%Cls for the PPD implying less variability and higher certainty in the results. The magnitude of the difference is estimated to be small for DM I and I/II. In contrast, 95%Cls that are very wide, indicate that there is less certainty due to the more possible variation in the actual precision of the effect. The interpretation of the point estimate is leading for the iudgement none-substantial.46 However, a point estimate with a substantial magnitude can have large variation by a broad 95% CI. The lower boundary of the 95% CI can even have a value that from the perspective of point estimates is judged as a small magnitude. For instance, a wide interval was shown in SR VI⁵⁷ on CAL regarding DM II (0.15<>1.84). The DiffM was 1.0, which can be interpreted as substantial.⁴⁶ This illustrates that a larger effect size and a bigger estimated magnitude do not necessarily indicate high reliability or precision, as a wide 95%Cl reflects considerable uncertainty around the true effect size. This highlights the importance of considering both effect sizes and CIs width when interpreting results, as large effects with wide CIs may not be clinically relevant. To acknowledge this uncertainty a prediction interval can be used.48 It relates to predicting the possible underlying effect in a new study that is similar to those in meta-analysis. Prediction intervals reflect the variation across different settings, including the expected effects in the future, thereby enhancing their clinical relevance.87 However, none of the included SRs reported a prediction interval. Heterogeneity was expected among the SRs, as study designs and details regarding the inclusion of the primary studies differ. Following the recommendations of the Cochrane Oral Health Group, this variance was addressed by applying a random-effects model, with the exception being when less than four studies were eligible for the meta-analysis. 88 However, the authors of included SR I¹⁴ reported all their outcomes by the use of the random -effects model, also up to three included studies. This could potentially lead to an overestimation of the between-study variance and resulting in a wider 95% Clandamore imprecise estimation of the overall effect size. In some of the meta-analysis performed, there was an obvious heterogeneity in the clinical outcome of the selected studies. For the secondary outcomes, the interpretation was based on Cohens d. if a SMD was provided. 47 However, the secondary outcomes were also reported as either a DiffM or WMD in one SR (VII). In these cases, direct comparisons is challenging due to variations in the approaches used to assess the influence of DM on periodontitis. In case the testing for heterogeneity was significant, the reader should exercise caution in using the DiffM/WMD as the exact measure of the effect.89

Citation matrix

A meta-review is a systematic collection and synopsis of multiple SRs. When examining multiple SRs, it is important to review the primary included studies and compare them to identify any potential overlap. For this meta-review a citation matrix (Online Appendix S2) was prepared to create a comprehensive overview of all underlying clinical studies as included in the selected SRs. This helps to ensure that the conclusions of the SRs drawn are based on a diverse range of studies. Overlap in primary studies has the potential to artificially inflate the accuracy of the analysis by overestimating the sample size and events. Including the same study multiple times in an analysis could influence the results and unwarranted weight. SRs primarily differ in terms of their research focus, inclusion criteria, and the publication date, with limitations arising from the inclusion of studies restricted to the time frame in which the search was conducted. For the latter the citation matrix was ordered by publication year to objectively show the potential of overlap. In the citation matrix of the present meta-review, 154 primary

studies are shown appearing in at least one of the seven included SRs. The primary studies mostly included in are Pinson et al. 1995, Dakovic et al. 2008 In four SRs, and De Pommereau et al. 1992, Morton et al. 1995, Firattli et al. 1996, Aren et al. 2003, Lalla et al. 2006, Al Khabbaz et al. 2013, Ismail et al. 2017 In three SRs. With an overlap of 3 to 4 primary study inclusions, it may be suggested that these studies provide valuable and reliable evidence in investigating the possible link between DM and periodontitis outcomes (Online Appendix S2). In addition, the authors found similar outcomes showing worse periodontal outcomes in DM patients compared to non-DM. Consistency across multiple reviews adds weight to the results and enhances the reliability of the conclusions drawn from the collective body of evidence. Conversely, the lack of overlap may contribute to the wide 95% Cls and the consequent limited precision. Nevertheless, there is currently no standardized methodological approach to manage the overlap in primary studies across multiple SRs for a meta-review.

Limitations

In this synthesis, both children and adolescents were included, which may limit the generalizability. This may affect the interpretation of the results, as genetic factors play a more prominent role in younger individuals for DM type I. Additionally, type II DM has a strong genetic component in adolescents, ¹⁰⁴ which may also influence the observed differences. This more fundamental research focus aimed to mitigate the potential confounding effects of genetic factors on DM – periodontitis link by including both children and adolescents. It is also important to recognize that both DM and periodontitis are multifactorial conditions, with their development involving a complex interplay of various components. ¹⁰⁵ Although almost all differences for PPD were significant, it is important to note that measurements errors of PPD typically range between 0.4–1.2 mm. ³⁶ Therefore, the clinical significance of statistical significance may still be limited.

Directions for future research

The heterogeneity among the studies should be considered as this may have an impact on the interpretation of the findings.⁴⁸ The variations in study design, measurement tools, and adjustment for confounding factors contribute to the heterogeneity observed. This underlines the need of delicate interpretation as some studies have suggested potential biases and confounding factors that could affect the accuracy of the findings. As a direction of the evidence for further research the actual effect size interpretation of differences and the manner of formulating conclusions on the link between the conditions seems of interest in the light of potential data spinning.¹⁰⁶

CONCLUSION

This meta-review summarized and appraised the available evidence from SRs with respect to the of DM on periodontal outcomes. There is a moderate certainty for a small to substantial difference regarding to CAL and a zero to substantial difference for PPD. For the secondary parameters there is weak evidence. Although statistically significant differences were observed heterogeneity was substantial and the clinical relevance of the differences vary in magnitude and its precision.

CLINICAL RELEVANCE

Scientific rationale for this analysis

DM and periodontitis are both common and chronic diseases that share risk factors. Despite the growing body of literature on the association between these conditions, the evidence on this relationship remains elusive and the clinical implication is unclear.

Principle findings

In periodontitis patients with DM the periodontal outcomes related to CAL and PPD are significantly greater than in non-DM. Although statistically significant differences were observed, the clinical relevance of these differences vary in magnitude and its precision.

Practical implications

Healthcare providers should be aware of shared risk factors of periodontal disease and DM and provide appropriate preventive management strategies to improve both health conditions.

Online Appendices



STATEMENTS

Acknowledgements

The authors acknowledge the support of Joost Bouwman, head librarian of the Academic Centre for Dentistry Amsterdam, who helped in the retrieval of the full-text articles. In addition, we want to thank J. de Lange.

Statement of ethics

This research has been approved by the ACTA Institutional review board, by reference number 2023-7560 and registered at the International Prospective Register of Systematic Reviews (PROSPERO) by number CRD42024550567.

Conflict of interest statement

The first author and co-authors declare that they have no conflicts of interest.

Funding sources

This review was self-funded by the authors and their institution.

Data statement

The data that supports the findings of this study are included in this article and the onlince appendices. Further enquiries can be directed to the corresponding author.

Author contributions

LPMW: contributed to conception and design, search and selection, analysis and interpretation, and drafted the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

SA: contributed to search and selection and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

REFERENCES

The papers included in this synthesis are highlighted in **bold** in the list.

- 1. Stöhr J, Barbaresko J, Neuenschwander M, Schlesinger S. Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Sci Rep.* 2021;11(1):1-2.
- 2. Telgi RL, Tandon V, Tangade PS, Tirth A, Kumar S, Yadav V. Efficacy of nonsurgical periodontal therapy on glycaemic control in type II diabetic patients: a randomized controlled clinical trial. *J Periodontal Implant Sci.* 2013;43(4):177. doi:10.5051/jpis.2013.43.4.177
- 3. Joseph R, Sasikumar M, Mammen J, Joseraj MG, Radhakrishnan C. Nonsurgical periodontal-therapy improves glycosylated hemoglobin levels in pre-diabetic patients with chronic periodontitis. *World J Diabetes*. 2017;8(5):213. doi:10.4239/wjd.v8.i5.213
- 4. Park Y. Why is type 1 diabetes uncommon in Asia? Ann N Y Acad Sci. 2006;1079:31-40. doi:10.1196/annals.1375.005
- 5. American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45:S17-S38.
- 6. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157.
- 7. Martínez-García M, Hernández-Lemus E. Periodontal Inflammation and Systemic Diseases: An Overview. *Front Physiol.* 2021;12. doi:10.3389/fphys.2021.709438
- 8. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005;366(9499):1809-1820.
- 9. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. *International Journal of Health Sciences (Qassim)*. 2017;11(2):72-80.
- 10. Kornman KS. Mapping the pathogenesis of periodontitis: a new look. . J Periodontol. 2008;79(8):1560-1568.
- 11. Albandar JM. Global risk factors and risk indicators for periodontal diseases. Periodontol 2000. 2002;29:177-206.
- 12. Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. *Ann Periodontol*. 2001;6(1):99-112.
- 13. Stankoa P, Izakovicova Hollab Lydie. Bidirectional association between diabetes mellitus and inflammatory periodontal disease: A review. . Biomedical Papers Medicine Faculty University Palacký Olomouc Czech Republic. 2014;158(1):35-38.
- 14. Zainal Abidin Z, Zainuren ZA, Noor E, Mohd Nor NS, Mohd Saffian S, Abdul Halim R. Periodontal health status of children and adolescents with diabetes mellitus: a systematic review and meta-analysis. *Aust Dent J.* 2021;66(S1):S15-S26. doi:10.1111/adi.12845
- 15. Zheng M, Wang C, Ali A, Shih YA, Xie Q, Guo C. Prevalence of periodontitis in people clinically diagnosed with diabetes mellitus: a meta-analysis of epidemiologic studies. *Acta Diabetol.* 2021;58(10):1307-1327.
- 16. Mirzaei A, Shahrestanaki E, Daneshzad E, et al. Association of hyperglycaemia and periodontitis: an updated systematic review and meta-analysis. *Journal of Diabetes & Metabolic Disorders volume*. 2021;20(2):1327-1336.
- 17. Preshaw PM, Alba AL, Herrera D, et al. Periodontitis and diabetes: a two-way relationship. Diabetologia . 2012;55(1):21-
- 18. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. *Nat Rev Endocrinol*, 2011;7(12).
- 19. Zhou X, Zhang W, Liu X, Zhang W, Li Y. Interrelationship between diabetes and periodontitis: role of hyperlipidemia. *Arch Oral Biol.* 2015;60(4):667-674.
- 20. Kumar M, Mishra L, Mohanty R, Nayak R. Diabetes and gum disease: The diabolic duo. Diabetes & Metabolic Syndrome: Olinical Research & Reviews. 2014;8(4):255-258.
- 21. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: A meta-analysis. *J Diabetes Complications*. 2006;20(1):59-68. doi:10.1016/j.jdiacomp.2005.05.006
- 22. Belting CM, Hiniker JJ, Dummett CO. Influence of Diabetes Mellitus on the Severity of Periodontal Disease. *J Periodontol.* 1964;35(6):476-480.
- 23. Campbell MJA. Periodontal disease in the diabetic patient and its treatment. Aust Dent J. 1967;12(2):117-122.
- 24. Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. *J Periodontol.* 2006;77(8):1289-1303.
- 25. Hugoson A, Jordan T. Frequency distribution of individuals aged 20–70 years according to severity of periodontal disease. *Community Dent Oral Epidemiol.* 1982;10(4):187–192.
- 26. Lavigne SE, Forrest JL. An Umbrella Review of Systematic Reviews of the Evidence of a Causal Relationship between Periodontal Microbes and Respiratory Diseases: Position Paper from the Canadian Dental Hygienists Association. Vol 54.; 2020. www.dentalcare.com/en-us/professional-
- 27. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: Methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc.* 2015;13(3):132-140. doi:10.1097/XEB.000000000000055
- 28. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of Observational Studies in Epidemiology: A Proposal for

- Reporting. JAMA. 2000;283(15):2008-2012. doi:10.1001/JAMA.283.15.2008
- 29. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA GROUP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 2009;6(7):e1000097. doi:10.14306/renhyd.18.3.114
- 30. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* 2007;7(I):10.
- 31. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int.* 2018;121(1):1027-1031.
- 32. Ryan R, Cochrane Consumers, Communication Review Group. Cochrane Consumers and Communication Review Group: data synthesis and analysis. 2013. Accessed December 23, 2023. http://cccrg.cochr ane.org
- 33. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1). doi:10.1186/s13643-016-0384-4
- 34. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ (Online)*. 2017;358. doi:10.1136/bmj.j4008
- 35. Van der Weijden FA, Slot DE. Efficacy of homecare regimens for mechanical plaque removal in managing gingivitis a meta review. *J Clin Periodontol*. 2015;42:S77-S91. doi:10.1111/jcpe.12359
- 36. MA Listgarten. Periodontal probing: what does it mean? J Clin Periodontol. 1980;7(3):165-176.
- 37. Löe H. The Gingival Index, the Plaque Index and the Retention Index Systems. J Periodontol. 1967;38(6):610-616.
- 38. Lang NP, Joss A, Orsanic T, Gusberti FA, Siegrist BE. Bleeding on probing. A predictor for the progression of periodontal disease? *J Clin Periodontol*. 1986;13(6).
- 39. Saxer UP, Mühlemann HR. Motivation and education. Monatsschr Zahnheilkd. 1975;85(9):905-919.
- 40. Mühlemann HR, Son S. Gingival sulcus bleeding—a leading symptom in initial gingivitis. *Helv Odontol Acta.* 1971;15(2):107-113.
- 41. Silness J, Loe H. Periodontal Disease in Pregnancy. II. Correlation between Oral Hygiene and Periodontal Condition. *Acta Odontol Scand.* 1964;22:121-135.
- 42. Lange DE, Plagmann HC, Eenboom A, Promesberger A. A. Klinische Bewertungsverahren zur Objektivierung der Mundhygiene [Clinical methods for the objective evaluation of oral hygiene]. *Dtsch Zahnarztl Z.* 1977;32(1):44–47.
- 43. Goldman HM, Cohen DW. Periodontal therapy. The CV Mosby Company, St Louis. Published online 1968:80-82.
- 44. Newman MG, Takei H, Klokkeveld PR, Carranza FA, editors. Carranza's Clinical Periodontology. Elsevier; 2014.
- 45. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: practical considerations for authors of overviews of reviews. *BMC Med Res Methodol*. 2021;21(1):1-14. doi:10.1186/S12874-021-01269-Y/FIGURES/4
- 46. Smiley CJ, Tracy SL, Abt E, et al. Evidence-based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. *Journal of the American Dental Association*. 2015;146(7):525–535. doi:10.1016/j.adaj.2015.01.026
- 47. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed.; 1988.
- 48. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (Updated August 2023). Cochrane: 2023.
- 49. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*. 2011;64(4):380-382.
- 50. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J.* 2008;336(7650):924–926.
- 51. van der Weijden FA, van der Sluijs E, Ciancio SG, Slot DE. Can Chemical Mouthwash Agents Achieve Plaque/Gingivitis Control? *Dent Clin North Am.* 2015;59(4):799–829.
- 52. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol*. 2013;66(2):151-157. doi:10.1016/j.jclinepi.2012.01.006
- 53. Jensen E, Allen G, Bednarz J, Couper J, Peña A. Periodontal risk markers in children and adolescents with type 1 diabetes: A systematic review and meta-analysis. *Diabetes Metab Res Rev.* 2021;37(1). doi:10.1002/dmrr.3368
- 54. Wu CZ, Yuan YH, Liu HH, et al. Epidemiologic relationship between periodontitis and type 2 diabetes mellitus. *BMC Oral Health.* 2020;20(1). doi:10.1186/s12903-020-01180-w
- 55. Rapone B, Corsalini M, Converti I, et al. Does periodontal inflammation affect type 1 diabetes in childhood and adolescence? A meta-analysis. *Front Endocrinol (Lausanne)*. 2020;11. doi:10.3389/fendo.2020.00278
- 56. Dicembrini I, Serni L, Monami M, et al. Type 1 diabetes and periodontitis: prevalence and periodontal destruction—a systematic review. *Acta Diabetol.* 2020;57(12):1405-1412. doi:10.1007/s00592-020-01531-7
- 57. Chávarry NGM, Vettore MV, Sansone C, Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. *Oral Health Prev Dent.* 2009;7(2):107-127.
- 58. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (Updated August 2023).* 2nd ed. John Wiley & Sons, 2019; 2023. doi:10.1002/9780470712184
- 59. Francke A, Smit M, de Veer AJE, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. *BMC Med Inform Decis Mak.* 2008;12(38).
- 60. Emrich LJ, Shlossman M, Genco RJ. Periodontal Disease in Non-Insulin-Dependent Diabetes Mellitus. J Periodontol.

- 1991;62(2):123-131. doi:10.1902/jop.1991.62.2.123
- 61. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. *Periodontol 2000*. 2007;44(1):127-153. doi:10.1111/j.1600-0757.2006.00193.x
- 62. Taylor JJ, Preshaw PM, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. *J Clin Periodontol.* 2013;40(SUPPL. 14):S113-34. doi:10.1111/jcpe.12059
- 63. Sanz M, Ceriello A, Buysschaert M, et al. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. *Diabetes Res Clin Pract.* 2018;137:231-241. doi:10.1016/J.DIABRES.2017.12.001
- 64. Sullivan GM, Feinn R. Using effect size-or why the P value is not enough. J Grad Med Educ. 2012;4:279-282.
- 65. Albandar JM. Global risk factors and risk indicators for periodontal diseases. Periodontol 2000. 2002;29(1):177-206.
- 66. Albandar JM. Periodontal diseases in North America. Peridontology 2000. 2002;29(1):31-69.
- 67. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. . *J Dent Res.* 2014;93(11):1045-1053.
- 68. Carrillo-Larco RM, Guzman-Vilca WC, Xu X, Bernabe-Ortiz A. Mean age and body mass index at type 2 diabetes diagnosis: Pooled analysis of 56 health surveys across income groups and world regions. *Diabet Med.* 2024;41(2):e15174.
- 69. Thorbert-Mros S, Cassel B, Berglundh T. Age of onset of disease in subjects with severe periodontitis: A 9- to 34-year retrospective study. *J Clin Periodontol*. 2017;44(8):778-783.
- 70. Reytor-González C, Parise-Vasco JM, González N, et al. Obesity and periodontitis: a comprehensive review of their interconnected pathophysiology and clinical implications. *Front Nutr.* 2024;11. doi:10.3389/fnut.2024.1440216
- 71. Iwashita M, Hayashi M, Nishimura Y, Yamashita A. The Link Between Periodontal Inflammation and Obesity. *Curr Oral Health Rep.* 2021;8(4):76–83. doi:10.1007/s40496-021-00296-4
- 72. Shetty B, Fazal I, Khan SF, et al. Association between cardiovascular diseases and periodontal disease: more than what meets the eye. *Drug Target Insights*. 2023;17:31-38. doi:10.33393/dti.2023.2510
- 73. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. New England Journal of Medicine. 2002;346(6):393-403. doi:10.1056/NEJMoa012512
- 74. Maboudi A, Akha O, Heidari M, Mohammadpour RA, Gheblenama P, Shiva A. Relation between Periodontitis and Prediabetic Condition. *J Dent (Shiraz)*. 2019;20(2):83–89. doi:10.30476/DENTJODS.2019.44928
- 75. Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ Canadian Medical Association Journal. 2008;179(3):229-234. doi:10.1503/cmaj.080012
- 76. Buchanan TA, Xiang AH. Gestational diabetes mellitus. *Journal of Clinical Investigation*. 2005;115(3):485-491. doi:10.1172/JCl24531
- 77. Campagna D, Alamo A, Di Pino A, et al. Smoking and diabetes: Dangerous liaisons and confusing relationships. *Diabetol Metab Syndr.* 2019:11(1). doi:10.1186/s13098-019-0482-2
- 78. Borgnakke WS. Modifiable risk factors for periodontitis and diabetes. Curr Oral Health Rep. 2016;3:254-269.
- 79. Borojevic T. Smoking and Periodontal Disease. *Materia Socio Medica*. 2012;24(4):274. doi:10.5455/msm.2012.24.274-276
- 80. Obradović R, Kesić LJ, Gašić J, Petrović M, Živković N. Role of Smoking in Periodontal Disease among Diabetic Patients Papel Del Hábito de Fumar En La Enfermedad Periodontal Entre Los Pacientes Diabéticos. Vol 61.; 2012.
- 81. Liu Y, Yu Y, Nickel JC, et al. Gender differences in the association of periodontitis and type 2 diabetes. *Int Dent J.* 2018;68(6):433-440. doi:10.1111/idj.12399
- 82. Loos BG, Needleman I. Endpoints of active periodontal therapy. *J Clin Periodontol.* 2020;47(S22):61-71. doi:10.1111/icpe.13253
- 83. Weijdijk LPM, Ziukaite L, Van der Weijden GA, Bakker EWP, Slot DE. The risk of tooth loss in patients with diabetes: A systematic review and meta-analysis. *Int J Dent Hyg.* 2022;20(1):145-166. doi:10.1111/idh.12512
- 84. Matuliene G, Pjetursson BE, Salvi GE, et al. Influence of residual pockets on progression of periodontitis and tooth loss: Results after 11 years of maintenance. *J Clin Periodontol.* 2008;35(8):685–695. doi:10.1111/j.1600-051X.2008.01245.x
- 85. Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. *Commun Stat Theory Methods*. 2017;46(14):6774-6781. doi:10.1080/03610926.2015.1134575
- 86. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. In: *Journal of Clinical Periodontology.* Vol 45. Blackwell Munksgaard; 2018:S162-S170. doi:10.1111/jcpe.12946
- 87. Inthout J, Ioannidis JPA, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open.* 2016;6:10247. doi:10.1136/bmjopen-2015
- 88. Sambunjak D, Nickerson JW, Poklepovic T, et al. Flossing for the management of periodontal diseases and dental caries in adults. *Cochrane Database of Systematic Reviews*. Published online December 7, 2011. doi:10.1002/14651858. cd008829.pub2
- 89. Van Der Weijden GA, Timmerman MF. A systematic review on the clinical efficacy of subgingival debridement in the treatment of chronic periodontitis. *J Clin Periodontol*. 2002;29:55-71.
- 90. Choi GJ, Kang H. Introduction to Umbrella Reviews as a Useful Evidence-Based Practice. *J Lipid Atheroscler*. 2023;12(1):3-11. doi:10.12997/jla.2023.12.1.3

- 91. Hennessy EA, Johnson BT. Examining Overlap of Included Studies in Meta-Reviews: Guidance for using the Corrected Covered Area Index. Res Synth Methods. 2020;11(1):134-145. doi:10.1002/jrsm.1390
- 92. Pérez-Bracchiglione J, Meza N, Bangdiwala SI, et al. Graphical Representation of Overlap for OVErviews: GROOVE tool. Res Synth Methods. 2022;13(3):381-388. doi:10.1002/JRSM.1557
- 93. Pinson M, Hoffman WH, Garnick JJ, Litaker MS. Clinical periodontology Periodontal disease and type diabetes mellitus in children and adolescents. *J Clin Periodomol*. 1995;22:118-123.
- 94. Dragana Dakovic, Milos D. Pavlovic. Periodontal Disease in Children and Adolescents With Type 1 Diabetes in Serbia. *Journal of Periodontology.* 2008;79(6).
- 95. de Pommereau V, Dargent-Paré C, Robert JJ, Brion M. Periodontal status in insulin-dependent diabetic adolescents. *J Clin Periodontol.* Published online 1992:628-632.
- 96. Morton AA, Williams RW, Watts LP. Initial study of periodontal status in non-insulin-dependent diabetics in Mauritius. *J Dent.* 1995;23:343-345.
- 97. Firatli E, Yilmaz O, Onan U. The relationship between clinical attachment loss and the duration of insulin-dependent diabetes mellitus (IDDM) in children and adolescents. *J Clin Periodontol*. 1996;23:362-366.
- 98. Aren G, Sepet E, Özdemir D, Dinççag N, Güvener B, Firatli E. Periodontal health, salivary status and metabolic control in children with type 1 diabetes mellitus. *J Periodontol*. 2003;74:1789–1795.
- 99. Lalla E, Park DB, Papapanou PN, Lamster IB. Oral Disease Burden in Northern Manhattan Patients With Diabetes Mellitus. *Am J Public Health*. 2004;94(5):755-758.
- 100. Al-Khabbaz AK, Al-Shammari KF, Hasan A, Abdul-Rasoul M. Periodontal health of children with type 1 diabetes mellitus in Kuwait: A case-control study. Medical Principles and Practice. 2013;22(2):144-149. doi:10.1159/000342624
- 101. Ismail AF, McGrath CP, Yiu CKY. Oral health status of chil-dren with type 1 diabetes: a comparative study. *J Pediatr Endo-crinol Metab*. 2017;30:1155-1159.
- 102. Hill AB. The Environment and Disease: Association or Causation? In: *Proceedings of the Royal Society of Medicine.*; 1965:295-300.
- 103. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: practical considerations for authors of overviews of reviews. *BMC Med Res Methodol*. 2021;21(1):140. doi:10.1186/s12874-021-01269-y
- 104. Srinivasan S, Todd J. The Genetics of Type 2 Diabetes in Youth: Where We Are and the Road Ahead. *Journal of Pediatrics*. 2022;247:17-21. doi:10.1016/j.jpeds.2022.05.044
- 105. Păunică I, Giurgiu M, Dumitriu AS, et al. The Bidirectional Relationship between Periodontal Disease and Diabetes Mellitus-A Review. *Diagnostics (Basel)*. 2023;13(4):681.
- 106. Yavchitz A, Ravaud P, Altman DG, et al. A new classification of spin in systematic reviews and meta-analyses was developed and ranked according to the severity. *J Clin Epidemiol*. 2016;75:56-65. doi:10.1016/j.jclinepi.2016.01.020

"When life gives you lemons ask for salt & tequila"

Fabiënne en Lotte

CHAPTER FIVE

The effect of diabetes on outcomes of non-surgical periodontal therapy

A systematic review with a meta-analysis and trial sequential analysis

L.P.M. Weijdijk, T.M.J.A. Thomassen, N.C. de Keyzer, E.E.J. Mayer, C. Valkenburg, G.A. Van der Weijden, D.E. Slot *International Journal of Dental Hygiene (submitted)*



ABSTRACT

Objective

The aim of this systematic review (SR) was to comprehensively and critically summarise and synthesize the available scientific evidence of the potential impact of diabetes mellitus (DM) on treatment outcomes in periodontitis patients undergoing non-surgical periodontal therapy (NSPT).

Methods

MEDLINE-PubMed and Cochrane-CENTRAL databases were searched from their inception up to April 2024 to identify eligible studies. The inclusion criterion was the availability of data for a group of patients with solely periodontitis and a group with both DM and periodontitis. Probing pocket depth (PPD) and clinical attachment level (CAL) were considered the primary outcomes of interest. Secondary parameters included gingival indices, plaque indices and gingival recession. Data from all included studies were presented descriptively, and a meta-analysis was conducted when quantitative methods were feasible.

Results

Screening of the 3574 papers resulted in 32 eligible publications, which reported 30 unique studies. Meta-analyses showed no differences of means in incremental changes from baseline to post-NSPT between the DM and non-DM groups for CAL and PPD. Moreover, the secondary outcomes also revealed no significant differences regarding the response to therapy. Based on the Trial Sequential Analysis (TSA) of these meta-analyses, the effect was found to be conclusive and reliable, indicating that additional data are unlikely to alter the summary effect.

Conclusion

Based on the evidence profile, it can be stated with moderate certainty that the difference in treatment outcomes of periodontitis patients following NSPT between the DM and non-DM group is insignificant.

INTRODUCTION

Periodontitis is a chronic multifactorial inflammatory disease that leads to the destruction of tooth-supporting structures.¹ Periodontitis ranks sixth among the world's most common diseases, affecting an estimated 11.2% of the global adult population.² It is characterized by irreversible damage to the root cementum, periodontal ligament, and alveolar bone, which can result in tooth loosening and eventual tooth loss.³ The primary etiological factor initiating and advancing periodontitis is the dental plaque biofilm, an organized aggregation of microorganisms.⁴ Treatment typically involves mechanical and/or ultrasonic debridement, known as non-surgical periodontal therapy (NSPT). This includes removing supra- and subgingival bacterial plaque and calculus, alongside providing oral hygiene instructions to patients.⁵ Due to the chronic nature of periodontitis, lifelong intensive supportive care is essential to prevent recurrence or further progression.⁶

The literature underscores the association between periodontitis and overall health, linking it to conditions such as cardiovascular disease, respiratory disorders, rheumatoid arthritis, and diabetes mellitus (DM)^{7,8} Individuals with DM face an elevated risk of developing and experiencing more severe periodontal disease.^{9 10} Moreover, the prevalence of DM is higher in populations with periodontitis compared to those without (non-DM).¹¹ It is presumed that there is a bidirectional relationship between DM and periodontitis.¹²

It is projected that by 2035, approximately 592 million individuals will be diagnosed with DM globally, 13 highlighting the need for a deeper understanding of its relationship with periodontitis. Recent findings from an umbrella review suggest that NSPT may contribute to improved glycemic control in type 2 DM.14 However, despite the substantial evidence, only two systematic reviews (SRs) have examined the impact of DM on clinical periodontal outcomes following NSPT. 9,16 The earlier SR, published in 2009, necessitates updating given the considerable advancements in the field. A more recent SR from 2019 suggests that DM does not significantly affect short-term treatment outcomes following NSPT, albeit with limitations in the parameters evaluated, particularly the absence of bleeding on probing (BOP), a critical indicator of gingival inflammation.^{16,17} Given that gingival inflammation is best assessed by BOP and plaque scores are essential secondary outcomes relative to the risk of periodontal diseases, 7 it is imperative to include these. Moreover, most studies in the SR reported only short-term clinical outcomes (up to 6 months), highlighting the need for more comprehensive, up-to-date investigations. 16,17 In addition, new studies appeared, and modern techniques can be applied by performing a meta-analysis. For instance, by utilizing Trial Sequential Analysis (TSA) to evaluate the balance between Type I and Type II errors and to determine when the effect size is sufficiently robust to remain unaffected by additional studies. Therefore, this SR aims to comprehensively summarize and synthesize current scientific evidence on the potential impact of DM on treatment outcomes in periodontitis patients undergoing NSPT.

METHODS

The preparation and presentation of this SR are in accordance with the Cochrane Handbook for Systematic Reviews¹⁸ and the guideline for meta-analysis and systematic reviews of observational studies in epidemiology (MOOSE).¹⁹ See Online Appendix S10.

Following the initial discussion between the members of the research team an 'a priori' protocol was developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)²⁰ (Online Appendix S7). This review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD42021227543. The institutional review board of the Academic Centre of Dentistry in Amsterdam (ACTA) also provided approval under the following number: 2022-43514.

Focused question

A precise review question was formulated utilizing the population, exposure, comparison, outcome, and type of study (PECOS)²¹ framework as follows:

What is the potential impact of DM [exposure] on clinical treatment outcomes [outcome] in periodontitis patients undergoing NSPT [population] compared to periodontitis patients without DM [comparison] as established from controlled observational studies [study]?

This question is based on the supposition that DM is strongly associated with periodontal disease²² and could therefore negatively influence the response to periodontal therapy.

Search strategy

A structured search strategy was designed to retrieve all relevant studies that evaluated the clinical effects of DM patients compared to non-DM periodontitis patients following NSPT. The search was designed by two reviewers (LPMW and DES). The National Library of Medicine, Washington, D.C. (MEDLINE-PubMed) was searched from its initiation to March 2024 for appropriate papers that answered the focused question. Table 1 provides details regarding the search approach employed. No limitations were applied regarding language or publication date in the search engine's strategy. The reference lists of the studies included in this review were hand-searched to identify additional potentially relevant studies. Additional grey literature was not sought nor examined.

Table 1

Search strategy used for PubMed-MEDLINE.

{[<exposure>] AND [<outcome>]}

<Exposure>

{<(Glucose Metabolism Disorders [Mesh]) OR (Diabetes Mellitus [Mesh] OR (Diabetes Mellitus) OR Diabetes OR diabet* OR (glucose metabolism disorders)>

<Outcome:>

<(Periodontitis [MeSH Terms] AND therapy) OR (periodontal therapy [MeSH Terms])) OR ((periodontal treatment) OR (periodontal therapy)>}

The asterisk (*) was used as a truncation symbol. The search strategy was customized according to the database being searched.

Screening and selection

Titles and abstracts (when available) from all studies were independently screened to select studies that potentially met the inclusion criteria. No language restrictions were imposed. Studies were categorized as 'eligible', 'not eligible', or 'questionable'. This process was performed independently by two reviewers (LPMW and TMJAT) using the web tool Rayyan, which expedites the initial screening of abstracts and titles using a process of semi-automation while incorporating a high level of usability. Disagreements concerning eligibility were resolved by consensus or if disagreement persisted, by arbitration through a third reviewer (DES). The papers that fulfilled all the inclusion criteria were processed for data extraction.

The eligibility criteria were as follows:

- Observational studies (case controls, cohort, RCT; only when randomization relates to way of treatment)
- Conducted in humans who were:
 - ≥ 18 years of age
 - Diagnosed with periodontitis and received NSPT
- Studies had to have at least two groups of patients:
 - Patients diagnosed with periodontitis and DM (or any synonym such as metabolic syndrome) and periodontitis
 - Patients diagnosed with periodontitis without DM
- Treatment outcomes should include change over time:
 - Primary outcome: probing pocket depth (PPD) and clinical attachment level (CAL)
 - Secondary outcome: gingivitis indices, plaque indices and gingival recession (REC)

The eligibility criteria were as follows:

- Patients with solely dental implants
- Additional treatments (laser, alternative adjuvants such as vitamin D)
- Additional surgical therapy
- Other systemic diseases
- Gestational DM as well as prediabetes

The reasons for exclusion after full-text reading were recorded (see Online Appendix S1). Thereafter, the selected full-text papers that fulfilled the eligibility criteria were identified and included in this SR. They were also processed for data extraction, methodological quality assessment and clinical, methodological and statistical heterogeneity. Both descriptive and quantitative methods were used for analysis (for details see Online Appendix S5+6).

Methodological quality assessment

Two reviewers (LPMW and TMJAT) independently scored the individual methodological qualities of the included studies using a comprehensive combination of the critical appraisal checklist for analytical cross-sectional studies, which was developed by the Joanna Briggs Institute,²⁴ the Newcastle Ottawa scale adapted for cross-sectional studies,²⁵ and the Risk of Bias In Non-randomized Studies – of Exposure (ROBINS-E) tool,²⁶ as reported by Van der Weijden et al.²⁷ Judgement of risk of bias is presented according to the seven domains as suggested by the ROBINS-E tool, which consists of:

- 1. Pre-assessment domains: bias due to confounding, bias in the selection of study participants, and bias in the classification of exposure
- 2. Post-assessment domains: bias due to deviations from the intended exposure, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported results

The judgments within each domain were carried forward to an overall risk of bias. A study was classified as having a *low risk* of bias when all domains were judged to have little risk of bias. A *moderate risk* of bias was assigned when one or more domains of the study were judged not to have a higher-than-moderate risk. A study was classified as having a *serious risk* of bias when one or more domains were scored as having serious risk. An overall *critical risk* of bias was scored when at least one domain was judged to be critical. The response option *no information* was assigned if the study was judged to be at serious or critical risk of bias and there was a lack of information in one or more key domains.^{24–27} If there was a disagreement between the two reviewers, then a consensus was achieved through discussion. If disagreement persisted, then a third reviewer (DES) was consulted. This judgment was decisive.

Data extraction

Independent data extraction was performed by two reviewers (LPMW and TMJAT) utilizing a specially designed standardized data extraction form. From the eligible papers, details on study design, demographics, DM diagnosis, NSPT and clinical treatment outcomes were extracted. If DM regulation was not clearly differentiated for good and poorly controlled, HbAlc levels were used to categorize the DM population. If the identified studies had multiple groups of subjects, only the groups fitting the selection criteria were included. Disagreement between the reviewers was resolved through discussion and consensus. If disagreement persisted, then the judgement of a third reviewer (DES) was decisive.

Outcomes

Clinical treatment outcomes were determined as primary and secondary outcomes:

- Primary outcomes were determined as follows (for details see Online Appendix S2.1):
 - PPD: periodontal pocket depth as measured from the gingival margin to the base of the periodontal pockets with the tip of the periodontal probe and expressed in mm.²⁸
 - CAL: clinical attachment level as measured with a periodontal probe from the cement-enamel joint (CEJ), or Relative Attachment Level (RAL) using a customized stent to the base of the pocket and expressed in mm.²⁹
- Secondary outcomes included the following indices, but are not limited to:
 - · Gingivitis indices:
 - BOP: Bleeding on Probing following Ainamo & Bay 1975.30
 - GI: Gingival Index following Löe & Silness 1963.31

- Plaque indices:
 - PI: Plaque index following O'Leary et al. 1972.³²
 - PI: Plague Index following Silness & Löe 1964.33
- Gingival recession (REC): gingival recession as measured clinically from the cementoenamel junction to the free gingival margin using a periodontal probe. It reflects the exposure of the root cementum and is measured in mm.^{34,35}

Details on additional indices which are included in the review can be found in the Online Appendix S2.2.

For all outcome parameters their means and standard deviation (SD) at baseline and follow-up were considered. When the SE was given the following was used to calculate the SD=SE×√N. If outcomes at multiple time points were reported, only the outcomes with the longest follow-up period but within 1 year were extracted. For those papers that provided insufficient data to be included in this paper, the first or corresponding author was contacted to request additional data.

Assessment of clinical and methodological heterogeneity

The factors utilized to assess the clinical heterogeneity of the various study outcomes were as follows: characteristics of participants (age, sex and continent), DM type (I or II), level of DM (controlled, uncontrolled, or undefined) and details regarding NSPT method (manual and/or ultrasonic). Factors employed to assess the methodological heterogeneity were diversity in study design details, subject characteristics, evaluation period, side effects and study funding. When clinical or methodological heterogeneity was presented across studies, sources of heterogeneity were investigated with subgroup or sensitivity analyses. Factors that were potentially relevant for subgroup analysis were DM-related details (type, duration and regulation).

Analysis

As a summary, a descriptive data presentation was utilized for all studies. A meta-analysis was performed if two or more studies presenting data on the same parameter could be included and if the individual studies provided an SD of the mean results. Thereafter, the difference of means (DiffM) as well as the associated 95% confidence interval and p-values for each parameter of interest was calculated between the two groups. As a guide for interpreting the results, a clinical relevance scale for interpreting the mean differences for CAL was used. Values of 0-0.2, >0.2-0.4, >0.4-0.6 and >0.6 were respectively classified as zero effect, small effect, moderate effect and substantial effect. 36 P-values \leq 0.05 were considered to be significant. Analysis was performed utilizing Review Manager version 5.3. 37 For a subsequent subgroup analysis, a meta-analysis was performed if more than one study could be included.

The authors of this SR anticipated that there would be considerable heterogeneity among the included studies, as study designs and details presumably differ. This variance was taken into consideration by primarily utilizing the random-effects model, with the exception being when less than four studies were eligible for meta-analysis. Otherwise, the fixed-effects model was utilized, as done by the Cochrane Oral Health Group.

Sensitivity analyses were undertaken to evaluate the effect of excluding studies based on specific aspects in the domain of clinical or methodological heterogeneity. Testing for publication bias per outcome was conducted, as proposed by Egger et al.³⁸ If the meta-analysis involved a sufficient number of trials to make a visual inspection of the funnel plot meaningful (a minimum of 10 trials), then these plots were employed as tools to assess publication bias.

The presence of asymmetry in the inverted funnel was regarded as suggestive of publication bias. 18,39,40 As planned, 'a priori', relative to DM status, a subgroup analysis was conducted. Subgroup analyses were also performed for pockets \geq 7mm and geographical regions. Trial sequential analysis (TSA) was applied to assess the robustness and reliability of the cumulative evidence and to reduce the risk of type I error. The required information size (RIS) and the trial sequential monitoring boundaries (TSMB) for benefit or futility were calculated. The RIS was calculated based on a type I error risk of $\alpha = 5\%$ and a type II error risk of $\beta = 0.20$, with a statistical test power of 80%. RIS accounted for heterogeneity and multiple comparisons. The Lan-DeMets version 41 of the O'Brien-Fleming function 42 was used for calculating the TSMBs. TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Copenhagen, Denmark) was used. $^{43-47}$

Assessment of statistical heterogeneity

Statistically heterogeneity was tested by the chi-square test and I^2 statistic. A chi-square test resulting in p<0.1 was considered an indication of significant statistical heterogeneity. As a rough guide to assessing the possible magnitude of inconsistency across studies, an I^2 statistic of 0%–40% was interpreted to indicate unimportant levels of heterogeneity. An I^2 statistic of 30%–60% may represent moderate heterogeneity and an I^2 statistic of 50%–90% may represent substantial heterogeneity. An I^2 statistic of greater than 75% was interpreted to indicate considerable heterogeneity and was further assessed with subgroup or sensitivity analysis.⁴⁸

Grading the 'body of evidence'

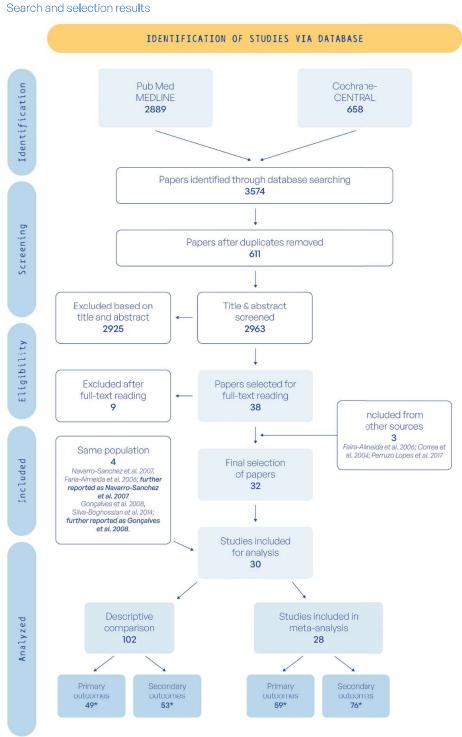
Two reviewers (LPMW and DES) rated the quality of the evidence and the strength of the recommendations according to the following aspects: study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias by utilizing the grading of recommendations assessment, development, and evaluation (GRADE) framework,⁴⁹ which provides a systematic approach for considering and reporting each of these factors. An overall rating of confidence in effect estimates was considered critical for the final recommendation.⁵⁰ Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, then the judgment of a fourth reviewer (GAW) was decisive.

RESULTS

Search and selection results

Figure 1 illustrates the search process. A total of 2963 unique articles were identified. The screening of titles and abstracts initially resulted in 38 papers. After full-text reading, 9 studies were excluded because they did not meet all the eligibility criteria. Reasons for exclusion are found in Online Appendix S1. Hand-searching of the reference lists revealed 3 additional suitable SRs.

Figure 1



Consequently, 32 papers were identified which reported on 30 unique studies, as data from the paper of *Navarro-Sanchez et al.* 2007⁵¹ and *Faria-Almeida et al.* 2006⁵² (further reported as *Navarro-Sanchez et al.* 2007) and *Gonçalves et al.* 2008⁵³ and *Silva-Boghossian et al.* 2014⁵⁴ (further reported as *Gonçalves et al.* 2008) concern the same study population. An overview of the included study IDS^{51,53,55-82} and their characteristics are presented in Table 2.

Methodological quality assessment

A summary of the methodological quality and potential risk of bias scores is presented in Online Appendix S3. Based on the assessment domains, the estimated potential risk of bias was low for three studies^{68,70,78}, moderate for most of the studies^{51,53,57,59,64-67,69,71-73,76}, serious for 12 studies^{55,58,60-63,74,75,77,79-81} and critical for two studies.^{56,82}

Assessment of clinical and methodological heterogeneity

Considerable heterogeneity was observed among the 30 included studies. Characteristics of study design, study population, details regarding NSPT, outcome parameters and other original conclusions are displayed in Table 2A. All studies used a prospective, observational, design. The evaluation period ranged from 1 month to 1 year. Most of the studies measured periodontal outcomes at 3-4 months. Three studies reported outcomes at 12 months. 55,77,78 In total, 1425 participants were included in this SR, consisting of 792 DM patients. Studies originating from the following world continents are present: nine in Europe, 51,55-57,60,61,67,70,79, 12 in Asia^{58,62,63,65,68,69,71,74–77,82} and nine in South America.^{53,59,64,66,72,74,78,80,81} Out of the 30 included papers, 26 studies specifically focused on DM type II. Two studies focused on DM type I^{55,65} and two other studies did not specify the type of DM.56,57 Only one paper differentiated between types I and II diabetes.⁷³ All studies include an non-DM group in satisfactory general health who were drawn from the population of the country where the study was performed. Regarding the level of periodontal disease, various criteria and diagnoses were used as parameters for inclusion. The majority of the studies excluded smokers, while five studies did include smokers^{51,57,61,66,67} and four other papers did not provide information on the smoking habits of the participants. 55,56,58,71 Some studies used a combination of ultrasonic and manual instrumentation as part of their NSPT while others relied solely on one or the other. Information on procedures such as the use of anesthesia, duration of instrumentation, subsequent use of rubber cups for polishing. follow-up supportive periodontal care and instructions regarding oral hygiene products was sparsely reported in the included studies (Online Appendix S4). In 6 of the 10 studies that provided data \geq 6 months, reported that supportive periodontal therapy was administered.

Table 2Overview of included studies processed for data extraction

Selection ID Authors Year Country RoB	N subjects Type of population Follow up	Sex (N males/females) Mean age (SD) Range in years	Intervention	Original parameters	Original authors conclusion
l Tervonen et al. 1991 Finland Rob: critical	N: 79 (Diabetes clinic Non-DM: Occupational Health service Follow up: 3-4m	DM type I/II N: 34 \$:10 \$:24 Mean age: ? Range: 18-51 DM duration: 8.9y (1.0) Non-DM N: 45 \$:14 \$:14 \$:14 \$:14 \$:31 Mean age: ? Range: 18-51	NSPT: SRP (mi, usi) Patient motivation, oral hygiene instructions, replacement of emergency restorations. The number of appointments varied between the patients depending on individual treatment need,	BOP, PPD	No significant difference could be observed in the response to NSPT treatment between diabetics and controls in either the decrease in gingival bleeding or the healing of periodontal pockets.
II Tervonen et al. 1997 Finland Rob: serious	N: 46 \(\rightarrow\) DM: Diabetes clinic and hospital Non-DM: Dental health care center clinic Follow up: 4w, 6m and 12m	DM type I N: 36 \$!? \$!? Mean age: 29.4 (3.7) Range: 24-36 DM duration: 16.9y (6.7) Non-DM N: 10 \$!? \$!? \$!? \$!? \$!? \$!? Range: 30.1 (3.8) Range: ?	NSPT: SRP Oral hygiene instruction and repeated when needed, removal of plaque retentive overhangs of fillings, restorative caries treatment.	PI, calculus, PPD, BOP, AL	No statistically differences could be observed between the diabetics and healthy controls at any examination.

=	N:40 ◊	DM type I+II	NSPT: SRP (mi + la, antiseptic)	API, PBI,	Patients with well controlled diabetes mellitus might
Christgau et al.		N: 20		BOP, PPD,	respond to non-surgical periodontal therapy
1998	DM:	8: o	Pretreatment phase: patient	PAL	similarly well as healthy controls.
Germany	Moderate to	♂ :12	motivation, oral hygiene instructions,		
	advanced	Median age: 54.5	supragingival scaling, placement of		
Rob: moderate	periodontitis	Range: 30-66	emergency restorations and removal		
	Referred patients to	DM duration (median):	of overhanging cervical crown		
	the Endocrine	11.5y	margins, extractions.		
	Department of				
	internal medicine	Non-DM			
		N: 20			
	Non-DM:	Q :12			
	Moderate to	d :8			
	advanced	Median age: 50.5			
	periodontitis	Range: 30-67			
	Referred patients to				
	the operative				
	dentistry and				
	periodontology				
	Follow IID: 2wk 4m				
2	N-11 O	DM type II	ASS. LASS	ROP PPD	Periodontal parameters improved in both groups
Sonoki et al 2006	>	N: 57)	
JOHN ST SIL 2000) <u>"</u>	4		
Japan			Oral hygiene instruction, extractions,		
	Moderate to severe	0 :4	treatment of caries, root canal or		
Rob: serious	periodontitis	Mean age: 60.4 (4.5)	other treatments.		
	Dental college	Range:?	Once weekly for supragingival scaling		
	department of	DM duration: ?	of one sextant for 6 weeks followed		
	periodontology		directly by subgingival scaling and		
		Non-DM	rootplaning of one sextant for 6		
	Non-DM:	N: 6	weeks		
		Q :4			
	Moderate to severe	d :2	Periodontal maintenance therapy at 1		
	periodontitis	Mean age: 49.2 (3.2)	month interval (usi)		
	Dental college	Range: ?			
	department of				
	periodontology				
	Follow up: 5.5-6.5m				

^	N: 30	DM type II	NSDT. SPD (mi + la)	PI ROP	Navarro-Sanchaz at al 2007
Novovo Conobos	0 7 ;	N:10			Short-toim noriodontal booling offor non-purgical
2+ 2 2007		⊇ c: • C		77 C, 77 C,	Sociological periodolical realing at the more great
et al. 2007	UNI:	7:)+ •	Pretreatment phase; provision or	CAL	periodontal treatment is similar between type z
Spain	Moderate	 ó	Intormation/Instructions on		diapetic and non-diapetic periodontal patients, both
	hronic	Mean age: 57.4 (6.1) ◆	periodontal disease and oral hygiene,		groups showed a significant improvement in clinical
Rob: moderate		Range:?	and supragingival prophylaxis.		periodontal status, and the presence of DM does
	Referred patient's	DM duration: 12y	Oral hygiene instruction, four 1-h		not appear to have a major effect on the success of
	periodontal clinic		session of scaling and rootplaning		periodontal therapy.
	school of Dentistry	Non-DM	over a maximum 4-week period,		
		N:10	supragingival prophylaxis.		Faria-Almeida et al. 2006
	Non-DM:	Q:7			Both patient groups improved clinically after basic
	Moderate	₫ :3			non-surgical periodontal treatment. Among the
	generalized chronic	Mean age: 56.4 (7.8) ◆			clinical variables studied, only probing depth showed
	periodontitis	Range: ?			a statistically significant difference between the
	Referred patient's)			groups after periodontal treatment between
	periodontal clinic				baseline and 3 and 6 months.
	school of Dentistry				
	0000				
	Follow up: 3, 6m				
<u></u>	N: 20	DM type II	NSPT: SRP (Ia)	PI, GI, PPD,	Non-surgical periodontal treatment using full-mouth
Da Cruz et al.		N:10		REC, CAL	root planing did not provide a significant difference
2008	DM:	\$:\$	Pretreatment phase: supragingival		in clinical responses between DM and NDM groups
Brazil	Generalized chronic	₫:?	biofilm was removed.		after 3 months of follow-up.
	periodontitis	Mean age: 47.10 (13.01)	Scaling and rootplaning in one		
Rob: serious	Olinic Dental School	Range: 30-70	session, 2h.		
		DM duration: 18.10y (11.37)	Oral hygiene instructions, plaque		
	Non-DM:		control at 2-week interval for 3		
	Generalized chronic	Non-DM	months.		
	periodontitis	N:10			
	Clinic Dental School	¿:♦			
		₫:?			
	Follow up: 3m	Mean age: 45.60 (7.24)			
		Range: 30-70			

	N- 40 A	DM type II	NSDT: SBD (mi + la)	VPI GRI	Non-surgical periodontal treatment improves the
	> \t : -!	CIVI (7) CO III	(b) (iii) (iii) (c)	, (0),	I volt satignat periodolitat a catilloricii ipioves and
Correa et al. 2008		N: 23		PPD, CAL,	clinical periodontal status.
Brazil	DM:	Q :14	Manual scaling and rootplaning with	BOP	
	Chronic	9 :9	anesthesia in four sessions.		
Rob: moderate	periodontitis	Mean age: 47.5 (7.2)	Oral hygiene instructions.		
	Olinic of	Range: 32-60 •	Plaque control twice a month for 3		
	periodontics,	DM duration: 9.96y (6.78)	months consisting of supragingival		
	School of Dentistry		plaque removal and reinstruction of		
		Non-DM	oral hygiene procedures.		
	Non-DM:	N: 26			
	Chronic	Q :12			
	periodontitis	9 :14			
	Periodontal clinic	Mean age: 41.6 (7.1)			
		Range: 30-60 ◆			
	Follow up: 3m				
III	N: 40	DM type II	NSPT: SRP (la)	VPI, GBI,	Gonçalves et al. 2008
Gonçalves et al.		N: 20		PPD, CAL,	In both groups, the periodontal therapy was
2008	DM:	Q :12	Scaling and rootplaning (1h).	BOP,	effective in improving most clinical parameters.
Brazil				presence of	
	Chronic	₫:⊗	Oral hygiene instructions, biofilm	suppuratio	Boghossian et al. 2014
Rob: moderate	periodontitis	Mean age: 45.80 (6.01)	control.		SRP associated with a rigorous maintenance pro-
	Olinic of	Range: 30-60	Plaque control twice a month for 3		gram improved the periodontal status at 3 months
	Periodontics for	DM duration: 9.85 (7.10)	months consisting of supragingival		evaluation in individuals with DM2 and inadequate
	Diabetic Patients,		plaque removal and reinstructions of		metabolic control compared with systemically
	School of Dentistry	Non-DM	oral hygiene procedures.		healthy individuals.
		N: 20			
	Non-DM:	0 :10			
	Chronic	ರೆ:10			
	periodontitis	Mean age: 43.65 (6.01)			
	Olinic for	Range: 30-60			
	PeriodonticsSc				
	hool of				
	Dentistry				
	Follow up: 3m				

×	N: 45	DM type II	NSPT: SRP (mi, usi)	PI, GI, PPD,	Poorly controlled and well-controlled diabetics
Dağ et al. 2009		(controlled/un-		GBI, CAL	might respond to non-surgical periodontal therapy
Turkey	DM:	controlled)	Pretreatment phase: oral hygiene		as well as non-diabetic patients.
	Chronic	N: 30	instructions, placement of		
Rob: serious	periodontitis	Q :12	emergency restorations and		
	Department of	♂:18	extraction of non-salvageable teeth.		
	Endocrinology	Mean age: 52.67 (After the therapy, patients did not		
		Range:?	receive periodontal interventions for		
	Non-DM:	DM duration: 7.23 (three months		
	Chronic				
	periodontitis	Poorly controlled			
	Department of	N:15			
	Periodontology,	\$:10			
	Faculty of	Q :5			
	Dentistry	Mean age: 53.13 (8.47)			
		Range: ?			
	Follow up: 3m	DM duration: 7.33 (2.76)			
		Good controlled			
		N: 15			
		8: o			
		₫:7			
		Mean age: 52,20 (7.67)			
		Range: ?			
		DM duration: 7.13 (1.84)			
		Non-DM			
		N:15			
		Q:7			
		₫:8			
		Mean age: 49.5 (7.61)			
		Range: ?			

×	N: 40	DM type II	NSPT: SRP	PI, PPD,	Patients with type 2 diabetes and chronic
Kardeşler et al.		(controlled/un-		CAL BOP	periodontitis exhibited similar clinical periodontal
2009	DM:	controlled)	Oral hygiene instructions and		improvements as their systemically healthy
Turkey	Chronic neriodontitis	N: 25 0 · 18	supragingival scaling and rootplaning		counterparts. Even patients in the poorly controlled
Rob: serious	Department of	d:7	On recall visits at 1 and 3 months		systemically healthy patients with periodontitis.
	Metabolic Diseases and Endocrinology, School of Medicine	Mean age: 52.88 ≬ Range: 44-64 DM duration: 7.38 ≬	supragingival plaque was removed and reinstructions were given.		
	Non-DM: Chronic	Poorly controlled N: 12			
	periodontitis Periodontology	4 :5			
	Clinic, School of Dentistry	Mean age: 50.25 (6.30) Range: 44-63			
	Follow up: 1, 3m	DM duration: 7.5 (4.40)			
		Good controlled			
		N:13 ♦:2			
		ਹੈ:11			
		Mean age: 55.31 (5.44)			
		Range: 44-64 DM duration: 6.69 (4.48)			
		0 0 2			
		NOT-UM N:15			
		9 : ¢			
		⊘ :9			
		Mean age: 51.31 (8.64) Range: 34-67			

	4 ()			0	-
×	\$ 00 : N	UM type II	NSFI: SKF (ml, usi)	FI, GI, FFU	Both groups showed an improvement in clinical
Kudva et al. 2010		N:15			parameters assessed at 3 months after nonsurgical
India	DM:		Scaling and rootplaning in a single		periodontal therapy.
	Moderate to severe	0::7	setting.		
Rob: serious	periodontitis	Mean age: ?			
	Diabetic Care and	Range: 40-60			
	Research Centre	DM duration: ?			
	Non-DM:	Non-DM			
	Moderate to severe	N:15			
	periodontitis	5:4			
	Diabetic Care and	₫: 5			
	Research Centre	Mean age: ?			
		Range: 40-60			
	Follow up: 3m				
IIX	N:30	DM type II	NSPT: SRP (mi + la)	PI, BI, GI,	Both patients groups improved clinically, after basic
Hungund et al.		N:15		PPD	non-surgical periodontal treatment. A statistically
2012	DM:	6:6	Pretreatment phase: provision of		significant improvement in clinical variables was
India	Moderate	₫:6	information/instructions on		found in both groups between baseline to three and
	generalized	Mean age: 50.46	periodontal disease, oral hygiene and		six months (P<0.05). The control group showed a
Rob: serious	periodontitis	Range:?	supra-gingival prophylaxis.		greater reduction in probing depth, as a result of
	Out-patient	DM duration: ?	Pretreatment phases were repeated		periodontal treatment.
	department,		at follow up examinations on 3 and 6		
	Hospital	Non-DM	months.		
		N:15			
	Non-DM:	5 : 6			
	Moderate	₫:6			
	generalized	Mean age: 40.73			
	periodontitis	Rande: ?			
	Out-patient				
	department				
	Periodontology,				
	Dental College				
	Follow up: 3, 6m				
	- CIC v 4F 0, CI-				

DM: One sossion with a time limit of 45 Connectized severe of 2:7 One sossion with a time limit of 45 Channelized severe of 2:7 One sossion with a time limit of 45 Periodontitis periodontitis Periodontitis of 2:7 Periodontitis of 2:7 Non-DM: N: 15 Non-DM N: 15 Cenduate clinic. DM type II NSPT: SRP (Ia) PPD, REC. Chlow up: 3, 6m N: 10 N: 10 PPD, REC. Oral registred chronic of 2:7 N: 10 N: 10 PPD, REC. DM: N: 20 ⟨ N: 10 N: 10 PPD, REC. Cenduate clinic O: 2 ⟨ N: 10 N: 10 PPD, REC. DM: N: 10 N: 10 N: 10 N: 10 DM: N: 20 ⟨ N: 10 N: 10 N: 10 N: 10 Range: 52 (8.72) Session Oral hygiene instructions NPI, CSI Non-DM: Non-DM Non-DM NPI, CSI NPI, CSI Moderate clinic Oral hygiene instructions NPI, CSI NPI, CSI DM: Oral hygiene instructions NPI, CSI	XIII Cirano et al. 2012	N: 31	DM type II (uncontrolled)	NSPT: SRP (usi)	PI, BS, CAL,	Full mouth ultrasonic debridement promotes clinical improvements in patients with type 2 uncontrolled
Page	Brazil	DM:) · · · · · · · · · · · · · · · · · · ·	One session with a time limit of 45		diabetes and generalized severe chronic
Carectarized Severe	Rob: moderate	chronic periodontitis	0 . : Mean age: 56.1 (11.7) Dange: 2	and subgingival tips.		
Non-DM Non-DM Non-DM Non-DM Ni i		Graduate clinic, University	DM duration: ?			
Centeralized severe \$\text{i} \cdots Generalized chronic of the control events of the control even		Non-DM:	Non-DM N: 15			
Perfodontitis Wean age: 54.7 (9.8)		Generalized severe chronic	♦: 5			
Follow up: 3, 6m		periodontitis Graduate clinic, University	nage: 54.7 (9. e: ?			
etal. Ni: 20 ∳ DM type II NSPT: SRP (Ia) PPD, REC. DM: Q:? under local anesthesia in a single CAL, Pt, GI Generalized chronic 0:? under local anesthesia in a single CAL, Pt, GI periodontitis Mean age: 52 (8.72) session. Oral hygiene instructions Non-DM: DM duration: 6.6y (4.17) Plaque control every 2 weeks interval Auring 3 months. Generalized chronic Non-DM Auring 3 months. Auring 3 months. Generalized chronic Q:? Auring 3 months. Auring 3 months. Generalized chronic Q:? Auring 3 months. Auring 3 months. Follow up: 3m Mean age: 31-6 (7.55) Range: 30-65 Auring 3 months. Follow up: 3m Mean age: 37-46 (7.55) Auring 3 months. Avpl. GBI. Moderate to 0: 12 ∮ Oral hygiene instructions, full mouth PPD, PAL Moderate to 0: 12 ∮ Oral hygiene instructions, full mouth April mouth Moderate to 0: 14 ∮ Auring advanced Pub. PAL Moderate to 0: 14 ∮		Follow up: 3, 6m				
vertail DN: N: 10 CAL, Pl, SI Generalized chronic ous 9:? under local anesthesia in a single perfodontitis cAL, Pl, SI Beneralized chronic ous Range: 30-65 (8.72) Oral hygiene instructions Oral hygiene instructions Non-DM: Non-DM: Oral hygiene instructions Oral hygiene instructions Periodontitis Non-DM: Oral hygiene instructions Pollow up: 3m Or: 2 Oral hygiene instructions Follow up: 3m Mean age: 41.6 (7.55) NSPT: SRP (mi, us) VPI, CBI, PDD, PAL Follow up: 3m Or: 2 Oral hygiene instructions, full mouth debridement in a single session using advanced NPD, PAL Moderate to Ors Ors Oral hygiene instructions, full mouth debridement in a single session using advanced Non-DM Non-DM: Non-DM: Ultrasonic scaling. PDD, PAL Non-DM: Oral hygiene instructions, full mouth debridement in a single session using advanced Non-DM Non-DM: Oral hygiene instructions, full mouth debridement advanced Oral hygiene instructions, full mouth debridement advanced Non-DM: Oral hygiene instructions, full mouth debridement advanced <	AIX	N: 20 ◊	DM type II	NSPT: SRP (la)	PPD, REC,	Periodontal therapy was effective to control the
ous Graduate Clinic A:: Graduate Clinic Range: 52 (8.72) DM duration: 6.6y (4.17) Fall 2014 Non-DM: N: 10 Graduate Clinic Range: 30-65 Follow up: 3m Mean age: 41.6 (7.55) Fall 2014 Ni. 10 Moderate to Mean age: 7.4 (14.80) Ni. 20 DM duration: 6.9 (4.17) Ni. 20 Oral hygiene instructions Aci: 7 Coral hygiene instructions Aci: 7 DM type I Ni. 20 Oral hygiene instructions, full mouth Moderate to Aci: 8 (4.38) Moderate to Mean age: 7.4 (14.80) Non-DM: Moderate to Non-DM advanced Ni. 21 DM duration: 2 Non-DM: Moderate to Non-DM advanced Ni. 21 DM duration: 3 Non-DM: Moderate to Non-DM advanced Ni. 21 DM duration: 3 Mean age: 7 DM duration: 4 DM duration: 3 Mean age: 7 DM duration: 4 DM duration: 4 DM duration: 5 DM duration: 7 Mean age: 7 DM duration: 7 Mean age: 7 DM duration: 7 DM duration: 7 Mean age: 7 Mean a	Camargo et al.	. 20	0::0	In I month cooling and rootalaning	CAL, PI, GI	periodontal disease. Significant improvement of
bus Graduate Clinic Range: 52 (8.72) session. Caracter Clinic Range: 30-65 Oral hygiene instructions	Brazil	Generalized chronic		ruininoutii saaiiii gana rootpianiing under local anesthesia in a single		Defload real status was found in both groups DM and NDM after 3 months, but no significant changes
Follow up: 3m		periodontitis	Mean age: 52 (8.72)	session.		were found between DM and NDM groups for gain of
Non-DM: during 3 months. during 3 months. Generalized chronic periodontitis \$\frac{9}{2} \cdot 2\$ \$\frac{1}{2} \cdot 2\$ Follow up: 3m \$\frac{7}{2} \cdot 2\$ \$\frac{1}{2} \cdot 2\$ Follow up: 3m \$\frac{1}{2} \cdot 2\$ \$\frac{1}{2} \cdot 2\$ Range: 30-65 NSPT: SRP (mi, usi) \$\frac{1}{2} \cdot 2\$ N: 20 \$\frac{1}{2} \cdot 2\$ \$\frac{1}{2} \cdot 2\$ DM: 20 \$\frac{1}{2} \cdot 2\$ \$\frac{1}{2} \cdot 2\$ erate \$\frac{1}{2} \cdot 2\$ \$\frac{1}{2} \cdot 2\$ hon-DM: \$\frac{1}{2} \cdot 2\$ \$\frac{1}{2} \cdot 2\$	ROD: Serious	Graduate Clinic	6.60	Oral hygiene instructions Plaque control every 2 weeks interval		attachments.
Generalized chronic periodontitis Non-DM Non-DM Non-DM periodontitis N: 10 Q:? N: 10 Graduate Clinic Q:? Mean age: 41.6 (7.55) NSPT: SRP (mi, usi) VPI, GBI, PPD, PAL Follow up: 3m Mean age: 30-65 NSPT: SRP (mi, usi) VPI, GBI, PPD, PAL Follow up: 3m Moderate to DM: N: 20 Oral hygiene instructions, full mouth debridement in a single session using manual instruments combined with periodontitis PPD, PAL erate advanced Mean age: 3 debridement in a single session using manual instruments combined with periodontitis Mon-DM: Ultrasonic scaling. Moderate to Non-DM: Moderate to Non-DM Non-DM V: 14 ◊ Moderate to Mon-DM: Mean age: ? Mean age: ? Mean age: ? Mean age: ? Mean age: ? Mean age: ?		Non-DM:		during 3 months.		
periodontitis N:10 Graduate Clinic 9:? Follow up: 3m		Generalized chronic	Non-DM			
Follow up: 3m		periodontitis Graduate Olinic	N:10			
tal. 2014 Mean age: 30-65 NSPT: SRP (mi, usi) VPI, GBI, PPD, PAL tal. 2014 DM type I NSPT: SRP (mi, usi) VPI, GBI, PPD, PAL DM: \$\Phi\$: 20 Oral hygiene instructions, full mouth debridement in a single session using advanced PPD, PAL erate advanced Mean age: 37.45 (14.38) manual instruments combined with debridement in a single session using manual instruments combined with advanced: 2 DM duration: 3 Non-DM: Moderate to Non-DM advanced N: 21 periodontitis \$\Phi\$: 14 \$ do: 7 \$ Mean age: 3		Follow up: 3m	d :?			
tal. 2014 N: 20 NSPT: SRP (mi, usi) VPI, GBI, PAL DM: Q: 12 ◊ Oral hygiene instructions, full mouth debridement in a single session using manual instruments combined with periodontitis PPD, PAL erate advanced Mean age: 37.45 (14.38) manual instruments combined with ultrasonic scaling. DM duration: ? Non-DM: Non-DM Non-DM Advanced N: 21 periodontitis Q: 14 ◊ Q: 14 ◊ Mean age: ? Mean age: ? Mean age: ?			Mean age: 41.6 (7.55) Range: 30-65			
PPD, PAL DM: 20 DM: 20 DM: 20 Oral hygiene instructions, full mouth Moderate to described with periodontitis Range: 37.45 (14.38) manual instruments combined with ultrasonic scaling. Non-DM: Moderate to Non-DM advanced N: 21 periodontitis Q: 14 ◊ Mean age: ? Mean age: ? Mean age: ? Mean age: ?	×	N: 4]	DM type I	NSPT: SRP (mi, usi)	VPI, GBI,	Both DM and NDM treatments produced similar
erate advanced Mean age: 37.45 (14.38) manual instruments combined with periodontitis Range:? Non-DM: Moderate to N:21 periodontitis \$\frac{\pi}{2}:14 \lambda \text{ Mean age: ?} Mean age:?	Buzinin et al. 2014	. 20	N: 20	Oral busions instructions full mouth	PPD, PAL	improvements in clinical parameters from baseline
advanced Mean age: 37.45 (14.38) manual instruments combined with periodontitis Range:? Non-DM: Moderate to Non-DM advanced N: 21 periodontitis Q: 14 ◊ Mean age:?	ivia i ayola	Moderate to	4 · 12 · √ 0 · 8 · ⟩	debridement in a single session using		were no statistically significant difference in
Kange: f Unitasoring scaling: DM duration: ? Unitasoring scaling: Non-DM N: 21 Q: 7 \$ Mean age: ? Mean age: ?	Rob: moderate	advanced	ge: 37.45 (manual instruments combined with		periodontal parameters between groups (P > 0.05)
			range: : DM duration: ?			
		Non-DM:				
		Moderate to	Non-DM			
		advanced periodontitis	N:21 0·14 A			
			₫:7 ◊			
		Follow up: 2, 3m	Mean age:? Range:?			

IVX	N: 52 (DM type II	NSPT: SRP (mi)	PPD, BOP,	Routine prophylaxes every 3 months significantly
López et al. 2013	•	N: 26		CAL, PI	improve periodontal health and prevent progression
Ohile	DM:	\$: l8	Pretreatment phase:		of chronic periodontitis in poorly controlled and well-
	Chronic	ರೆ:8	extractions of hopeless teeth		controlled T2DM.
Rob: moderate	periodontitis	Mean age: 58.9 (8.9)	and emergency restorative		
	Public Health	Range: 47-67	treatments of caries lesions.		
	Center, Dental	DM duration: ?	Oral hygiene instructions,		
	Center, Hospital		supragingival scaling using an		
		Non-DM	ultrasonic scaler and crown		
	NDM:	N: 26	polishing.		
	Chronic	Q :19	At each recall visit oral hygiene		
	periodontitis	₫:7	is checked and reinforced and		
	Public Health	Mean age: 55 (7.6)	dental prophylaxis were		
	Center, Dental Center, Hospital	Range: 45-70	performed.		
	- - - - -				
\	FOIROW UP: 5, 0, 9111	\(\cdot \	NCDT. CDB (mici)		The improvement of poriodoutal parameters
Kara et al. 2015		N:15		BOP. CAL	showed that T2DM patients can benefit from
Tirkav	Š	0.7	Scaling and rootplaning in 2		neriodontal therapy, as well as non-diabetic patients
	Chronic	 	sequential visits in 7 days using the		With periodontitis.
Rob: moderate	periodontitis	Mean age: 42 8 (7 40)	combination of hand instruments and		
	Department of	Range: 34-58	ultrasonic devices.		
	Metabolic Disease,	DM duration: 6.93 (3.66)	No adjunctive therapy.		
	School of Medicine		Oral hygiene instructions,		
		Non-DM	supragingival scaling were performed		
	Non-DM:	N: 15	during follow-up monthly.		
	Chronic	Q:10			
	Periodontitis	d :5			
	Periodontology	Mean age: 47.73 (7.08)			
	department,	Range: 33-56			
	Faculty of Dentistry				
	Follow up: 1, 3m				

	< L 	=	: · · · · · · · · · · · · · · · · · · ·		
Kaur et al. 2015	> 0 2	Controlled/un-	1407 . UAT (III, dai)	FI, GI, FFD, CAL. PESA.	nor surgical periodor rai merapy improved periodontal health in patients with type 2 diabetes.
India	DM:	controlled)	Oral hygiene instructions, four SRP	PISA, BOP	However, patients with poor baseline glycemic
	Moderate or severe	N:50 \$	sessions over a maximum of 2 weeks		control had less clinical improvement than those
Rob: low	chronic	♀ :28 ◊	manual and ultrasonic. Oral hygiene		without diabetes and those with good glycemic
	periodontitis	♂ : 22 ◊	instructions were reviewed at each		control.
	Department of	Mean age: 51.82 (visit and additional supportive SRP		
	Periodontics and	Range:?	was done when necessary.		
	Oral Implantology, Institute of Dental	DIVI duration: 6.57 (
	Science	Poorly controlled			
		N: 27			
	Non-DM:	\$:15			
	Moderate or severe	♂ :12			
	chronic	Mean age: 50.96 (6.43)			
	periodontitis	Range: ?			
	Department of	DM duration: 8.41 (6.25)			
	Periodontics and	Good controlled			
	Oral implantology,	N: 23			
	Institute of Dental	Q:1 0			
	Science	♂ :13			
	Follow up: 3, 6m	Mean age: 52.83 (5.04)			
		DM duration: 8.76 (6.71)			
		Non-DM			
		N: 25			
		01:5 •			
		Q: Q			
		Mean age: 51.56 (5.91) Range: ?			
XIX	N:70 ◊	DM type II	NSPT: SRP (mi, usi)	PI, GI, PPD,	A significant reduction in plaque index, gingival
Pannicker et al.		N: 35		CAL	index, probing pocket depth and clinical attachment
2015		4:16	Scaling and rootplaning		level in both groups occurred at 3 weeks, compared
India	Chronic	6 :,0	Monitoring oral hygiene weekly		With baseline.
Roh: moderate	periodontitis Department of	Mean age: 43.29 (8.40) Dang: 30.40			
	Periodontics	Nalige: 50-60			
	Non-DM:	Non-DM			
	Chronic	N: 35			
	periodontitis	\\ \\ \ :20			
	Periodontics	♂ :15 Mean age: 44.09 (6.87)			
		Range: 30-60			
	Follow up: 6wk				
	-				

	< ()	=		(
×	◇ 04 : N	DIMITYPE II	NSFI: SKF (ml, usl + la)	Ţ, Œ	iviean probing depth, clinical attachment level,
Doğan et al. 2016		N: 20		PPD,	bleeding on probing, plaque index and gingival index
Turkey	DM:	6: 	Scaling and rootplaning via the	CAL,	levels were significantly lower among both groups
	Chronic	♂:11	use of manual scalers and	BOP	after non-surgical periodontal therapy.
Rob: low	periodontitis	Mean age: 47.35 (4.97)	curets with local anesthetic		
	Department of	Range: ?	twice per week, every		
	Periodontology,	DM duration: 4.05 (0.76)	appointment lasted 45-60		
	Faculty of Dentistry		minutes.		
		Non-DM			
	Non-DM:	N: 20			
	Chronic	Q:1 0			
	periodontitis	♂ :10			
	Department of	Mean age: 49.05 (4.71)			
	Periodontology, Faculty of Dentistry	Range:?			
	Follow up: 6wk	\(\cdot \	000		A++ho ond of one month work to the order
Mishra et al. 2016	> 07 :	N:14		PPD	decreased significantly compared to the pre-
India	DM:	4:7	Scaling and rootplaning		treatment values in both chronic periodontitis group
	Chronic	₫:7			and chronic periodontitis with diabetes mellitus
Rob: moderate	periodontitis	Mean age: 48.07 (5.54)			group, but on inter-group comparison it remained
	Department of	Range: 30-65			statistically insignificant.
	Periodontics and	DM duration: ?			
	Oral Implantology,				
	College of Dental	Non-DM			
	Science and	N:14			
	Hospital	5 :6			
		₫ :8			
	Non-DM:	Mean age: 41.71 (8.06)			
	Chronic	Range: 30-65			
	Periodontitis				
	Department of Periodontics and				
	Oran Implantology, College of Dental				
	Science and Loopital				
	Follow up: 1m				

IIAA	« ° ° ° ′ ′ ′ ′ ′ ′ ′ ′ ′ ′ ′ ′ ′ ′ ′ ′	1	TOOL TOOL	- 40	
Ahrenetal 2015	>	N:30		ROP PI	portionalities with dispetes mellitus) showed a
Brazil	. NA.	0.17	For in to sive assertions of small and in the principle of the principle o	<u>-</u>	significant improvement of the parameters apart
DIGZII	Olvi.	ت. تا. بر	rout to six sessions of scannig and		signincal chropmont lovel which issues to the
-	=======================================				Horn dimical actacimment level, which miproved but
Rob: moderate	periodontitis	Mean age: 55.43 (8.56)	Pretreatment phase: oral hygiene		not statistically after periodontal therapy in
		Range: 38-68 ◆	instructions, oral prophylaxis and		diabetics with chronic periodontitis.
	Non-DM:	DM duration: 5y ◆	supragingival scaling.		
	Chronic		Post-treatment phase for a period of		
	periodontitis	Non-DM	4wk: weekly plaque control (oral		
		N: 30	hygiene instructions, supragingival		
	Follow up: 1m	9 :14	scaling and prophylaxis).		
		ુ : 16			
		Mean age: 44.47 (9.17)			
		Range: 21-64 •			
IIIXX	N: 52 ◊	DM type I + II	NSPT: SRP	PI, BOP,	Periodontal treatment is effective in controlling
Perruzo Lopes et		N: 4] ◊		PPD, CAL	inflammation in patients with diabetes mellitus I and
al. 2017	:. 	♀ :20 ◊	Instruction and motivation		diabetes mellitus 2.
Germany	Chronic	ೆ :21 ◊	about oral hygiene, supra-and		
	periodontitis	Mean age: 53.70 ◊	subgingival scaling, root planing		
Rob: moderate	Invited by radio and	Range:?	and coronal polishing.		
	TV broadcast and	DM duration: ?	Patients received reinforcement		
	treated at a		of oral hygiene and maintenance		
	dentistry clinic	DM type I	periodontal therapy.		
		Z-1.Z	2a amoxicillin as antibiotic		
	Non-DM.	↓	prophylaxis 1h hefore the		
		→ (· · · · · · · · · · · · · · · · · ·			
	CITOTIC	•6:,o	appointment was presonded for		
	periodonuus	Mean age: 42.5 (16.8)	diabetic patients		
	Invited by radio and	Range:?			
	IV broadcast and	DM duration: ?			
	treated at a				
	dentistry olinic	DM type II			
		N: 27			
	Follow up: 6m	€:15◆			
		0.12◆			
		Mean age: 59.5 (9.7)			
		Rande: 2			
		Nange. : DM duration: ?			
		Non-DM			
		F.Ż			
		♦ :6♦			
		Mean ade: 447 (127)			
		Rande: 7			

XXIV	OCI -IN		NSDT: SPD (Ia)	DI GI BOD	A statistically significant reduction in all the clinical
Sundaram et al.	0 2 :	(controlled/un-		PPD CAL	narameters within the groups was found except for
2017	DM:	controlled)	Scaling and rootplaning under		the CAL in non-diabetic patients. The subjects with
India	Outpatient clinic of	N:80 (local anaesthesia, oral hygiene		DM had significantly more clinical attachment loss
	the department of	5:5	instructions		than nondiabetic subjects.
Rob: serious	periodontics,	₫:?	Professional plaque programme		
	Dental College and	Mean age: ?	(twice a month for 3 months)		
	Hospital	Range:?	and reinstructions of oral		
		DM duration: ?	hygiene procedures.		
	Non-DM:				
	Outpatient clinic of	Poorly controlled			
	the department of	N: 40			
	periodontics,	¿:.�			
	Dental College and	Q ::5			
	Hospital	Mean age: ?			
		Range: 3			
	Follow up: 3m	DM duration: ?			
		Well controlled			
		N: 40			
		¿∶ 			
		₫:?			
		Mean age: ?			
		Range:?			
		DM duration: ?			
		NOT-UNI			
		.; .; Q.:?			
		Mean age: ?			
		Range: ?			

\XX\	N: 60	DM type II	NSPT: SRP	PPD, CAL,	Initial periodontal therapy seems to be beneficial in
Gayathri et al.		N: 30		$\overline{\mathbb{Q}}$	reducing serum NO levels along with periodontal
2019	DM:	\$:16	Oral hygiene instructions,		parameters in CP patients with or without T2DM.
India	~	ਹੈ:14	scaling and rootplaning.		
	200 200 200 200 200 200 200 200 200 20	Mean age: ?	Recalled after 4 weeks.		
		kange. sr-/u DM duration: ?			
	\$ t :	NOI			
		\$1.5			
		9 :18			
		Mean age:? Range: 31-70			
IXXX	N: 60	DM type II	NSPT: SRP	PPD, CAL,	NSPT was effective in improving clinical parameters,
Ahuja et al. 2019		N:30 0:16	Soeling and roothlaning ora	N C	increasing GCL, reducing serum leptin levels, and
5	Outpatient	4 : [0]	hygiene instructions. Recall		and OP with T2DM.
Rob: moderate	Department of	Mean age: 41.33 (11.87) ◆	visits at 3 and 6 months,		
	Periodontics and	Range: 24-60 🔷	supragingival plaque and oral		
	Implantology, Dental College and	DM duration: ?	nygiene re-instructions.		
	Research	Molon			
		N: 30			
	Non-DM:	Ç			
	Outpatient Dopostmont of	<u>~</u>			
	Periodontics and	0.1/ Mosp ago: E2 47 (8.23) ▶			
	Implantology.	Neal age: 32.47 (6.23)			
	Dental College and	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\			
	Research				
	Follow up: 6m				
XXVII	N: 60	DM type II	NSPT: SRP (usi, mi + la)	PPD, CAL,	A decline in the values for all the parameters when
Pragada et al.	Ĉ	N: 30	- - -	QIPI	evaluated with baseline values 6 weeks after the
2019 Sipal	DIVI:	··· ··· ··· ··· ··· ··· ··· ··· ··· ··	Scaling and rootplaning and oral		periodontal treatment, once again substantiating
II lula	Department of	0::	nygierie instructions.		une signimoanice of priaseri unerapy.
Rob: serious	Dental College and	Neal age:			
	Hospital.	DM duration: ?			
	Non-DM:	Non-DM:			
	Periodontics,	N. 30 •••			
	Dental College and				
	Hospital.	Mean age: ?			A H C
	Follow up: 6w	Range: 30-60			

PPD, CAL, Type 2 diabetic subjects and systemically healthy subjects with mild-to-moderate periodontitis responded similarly to the proposed FMD protocol for up to 1 year.	Pi, Gi, PPD, DM patients might respond to non-surgical coal periodontal therapy similarly well to non-diabetic patients. There were no significant differences in the treatment outcomes among the groups according to most of the clinical parameters measured. In conclusion, based on the results yielded by the present study, the periodontal therapy outcome in patients with diabetes does not seem to be significantly affected by the level of glycemic control.
NSPT: SRP (mi, usi) Pre-treatment (removal of plaque and calculus, extraction, provisional restoration, and filling overhang removal), scaling and rootplaning, CHX solution, pocket irrigation, oral hygiene instructions. Supportive posttherapy of plaque control, relinstructions, subgingival debridement (at 3, 6, 9 and 12m).	NSPT: SRP (mi, usi) Scaling and rootplaning in one or two sessions 1h, oral hygiene instructions.
DM type N: 26 9:15 0:11 Mean age: 57.9 (8.1) • Range: 36-69 • DM duration: 7.7y Non-DM N: 28 9: 21 0: 7 Mean age: 44.8 (11.7) •	Pontype II (controlled/un-controlled/un-controlled/un-controlled/un-controlled) N: 61 \$\int : 26 \\ \phi : 35 \\ \phi \\ \text{Mean age: 59.3 }\\ \text{Range: ?}\\ \text{DM duration: ?}\\ \text{DM duration: ?}\\ \text{Poorly controlled }\\ \phi : 16 \\ \phi : 16 \\ \phi : 16 \\ \phi : 16 \\ \phi : 10 \\ \phi : 19 \\ \text{Mean age: 60.5}\\ \text{Range: ?}\\ \text{DM duration: ?}\\ \text{Good controlled }\\ \phi : 19 \\ \text{Mean age: 60.5}\\ \text{Range: ?}\\ \text{DM duration: ?}\\ DM duration: ?
N: 54 () DM: Referred patients to the Dental Clinic of the Federal University Non-DM: Referred patients to the Dental Clinic of the Federal University Follow up: 12m	N: 92 DM: Hospital patients who were regular controlled by an endocrinologist Non-DM: referred patients to a periodontist Follow up: 3m
XXVIII Almeida et al. 2019 Brazil Rob: low	XXIX Mirnic et al. 2022 Servie Rob: serious

	Nort-DM N: 31 • 13 • 18 Mean age: 57.4 Range: ?			
N:30	DM type II N: 15	NSPT: SRP (la)	PI, GI, PPD, CAL	After NSPT, there was a reduction in clinical parameters in both groups.
Dental College and Hospital	ď :? Mean ade:?	sessions under local anaesthesia.		
	Range:? DM.duration:?			
Non-DM:				
Dental College and	Non-DM			
Hospital	N: 15			
Follow up: 6w	4 ∵.? ₫ :??			
	Mean age:?			
	Kange: ?			

OT: $\phi = Calculated$ by the authors of this review based on the presented data in the selected paper, DM: diabetes mellitus, Non-DM: no diabetes mellituss, PI: plaque index, GBI: gingival bleeding index, GI: gingival favel, AL: attachment level, AL: attachment level, REC: gingival recession, VPI: visible plaque index, BS: bleeding score, PAL: probing attachment level, AL: attachment level, REC: gingival recession, VPI: visible plaque index, BS: bleeding score, PAL: probing attachment level, PESA: periodontal h: hours, w: weeks; m: months, y: years, ?: unknown/not reported, NSPT: non-surgical periodontal treatment, SRP: scaling rootplaning, mi: manual instrumentation, usi: ultrasonic instrumentation, la: local anesthesia, epithelial surface area PISA: periodontal inflamed surface area

Side effects and industry funding

The included papers did not report any adverse events or side effects. 18 studies were not sponsored or did not provide any information regarding study funding. The other 12 studies reported being supported by a university or a non-profit grant organization.

Study results Description of findings

Online Appendix S5 describes and summarizes the statistical differences as reported in the original studies between DM patients and non-DM individuals regarding the primary and secondary outcome parameters. In detail, the majority of the comparisons revealed no statistically significant differences in the results of NSPT between the two groups on any of the parameters of interest. With respect to the primary outcomes, 22 comparisons concerning PPD in DM type II, five found statistical difference in favor of the non-DM. For the secondary outcomes, a higher reduction in the gingivitis indices was obtained in favor of non-DM in 1/3 comparisons on DM type I and 7/21 for DM type II. For plaque, no differences were found between non-DM and DM type I, while 5/19 studies reported higher reductions in non-DM compared to DM type II.

Meta-analysis

Two studies^{55,56} provided data for the percentages of sites concerning PPD and CAL and could therefore not be included in the meta-analysis. Study XV⁶⁵ did not provide overall data, so their data were only included in sub-analysis for deep pockets (>7mm). Due to the lack of standard deviation or standard error of the mean for incremental scores in some studies, only 18 studies within 21 comparisons were included for the meta-analysis of PPD and 15 studies included 18 comparisons for CAL. Sub-analysis for the primary outcomes was performed for good and poorly controlled DM. It was not possible to differentiate between DM type I and type II based on the extracted data. Meta-analysis for the secondary outcomes was performed on % plaque, PI, BOP, GI, GBI and REC. For details see online appendix S6 and S7.

Overall scores Primary outcomes

There was a significant difference of means between DM and non-DM for PPD at the baseline (DiffM=0.21, p=0.004, 95% CI [0.07<>0.35]) and end scores (DiffM=0.16, p=0.01, 95% CI [0.03<>0.29]) in favor of non-DM. The same was found for CAL at baseline (DiffM=0.27, p<0.0001, 95% CI [0.13<>0.41]) and end data (DiffM=0.26, p=0.02, 95% CI [0.05<>0.47]) (Online Appendix S7). However, the mean PPD reduction following treatment in the DM group was not significantly different from the non-DM group DiffM=0.02 (p=0.57, 95% CI [0.06<>0.10]) (Online Appendix S7.3). The mean CAL gain in the DM group was also not significantly different from non-DM DiffM=0.06 (p=0.38, 95% CI [-0.19<>0.07]) (Online Appendix 7.6). Table 3 summarizes the detailed outcomes of the meta-analysis performed on the outcome parameters.

Sensitivity analysis was conducted to evaluate the influence of a single study on the overall effect estimate by stepwise omitting, one by one, each of the studies included in the meta-analysis and re-evaluating the summary effect estimates. Sensitivity analysis did not reveal any specific effect on the observed outcomes.

Trial Sequential Analysis

Figure 2A illustrates that the cumulative Z-curves crossed the futility boundary after including three studies for PPD, indicating a low likelihood of significant differences between the two treatment arms, making the addition of trials potentially ineffective. The futility was confirmed after including four studies, when the sample size surpassed the required meta-analysis sample size, leading to the confident inference that there was no difference in effect between the groups. Regarding CAL, the Z curves crossed the futility boundary after the inclusion of ten studies and the ineffectiveness of additional trials was confirmed after 17 studies (Figure 2B). It can be confidently inferred that there was no difference in effect between the groups, despite three Z-values exceeding 1.96 in the preceding analysis. Based on the TSA of these meta-analyses, the effect was found to be conclusive and reliable, indicating that additional data are unlikely to alter the summary effect.^{44,83}

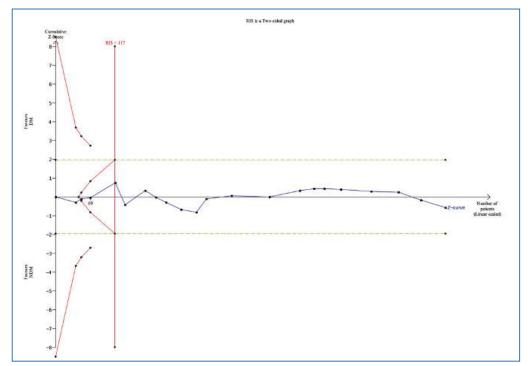
Secondary outcomes

At baseline, a significant difference was found for GI (DiffM=0.13, p=0.003, 95% CI [0.05<>0.22]). There was also a small but significant difference found post-NSPT for GI (DiffM=0.18, p<0.0001, 95% CI [0.10<>0.25]) and BOP (DiffM=4.64, p=0.005, 95% CI [1.39<>7.89]). For the other secondary parameters, no significant differences were found. For details Table 3 and Online Appendix S7.

Figure 2 Trial Sequential analysis

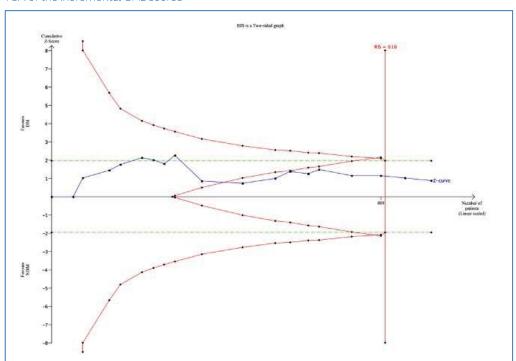
The cumulative blue Z-curves were constructed with each cumulative Z-value calculated after including a new trial according to publication date. Crossing of the two-sided Z=1.96 indicates a traditionally significant result. Crossing of the red trial sequential monitoring boundaries is needed to obtain reliable evidence adjusted for random error risk. Z-curves not crossing Z=1.96 indicate absence of evidence if the information size is not reached or lack of the predefined intervention effect if the information size is not reached (81). The green dotted lines represent the traditional boundary. The vertical red line represents the estimated heterogeneity-adjusted required information size, the number of participants needed for the meta-analysis sample size.

Figure 2ATSA of the incremental PPD scores



The user-defined mean difference effect was set at 0.31, with a Type 1 error of 5.0% and a power of 80%. The estimated inconsistency was $l^2 = 88\%$, and the estimated diversity was $D^2 = 94\%$.

Figure 2BTSA of the incremental CAL scores



The user-defined mean difference effect was set at 0.21 (34) with a Type 1 Error of 5.0%, and a power of 80 %. The estimated inconsistency was $I^2 = 94$ %, and the estimated diversity was $D^2 = 979$ %.

Table 3

Meta-analysis for the baseline, end and incremental data evaluating the effect of non-surgical periodontal therapy on the clinical parameters of periodontitis. 3A: probing pocket depth (PPD), 3B: clinical attachment level (CAL), 3C: bleeding scores (BS), 3D: gingival indices, 3E: plaque indices, 3E: gingival recession (REC)

	Table 3A PPD								
	Measurement moment	Included studies #	M	DiffM (mm)	Test overall	werall	Test for he	Test for heterogeneity	For details see Figure/Appendix
		comparisons)		IO %56	p-value	l² value (%)	p-value	
	Overall	32	Random	0.21	[0.07<>0.35]	0.004	%16	<0.00001	S7.1
	PPD >7mm	4	Fixed	1.41	[-0.53<>3.35]	91.0	72%	0.01	S7.37
	DM well controlled	14	Random	0.23	[0.05<>0.42]	0.01	76%	<0.00001	87.25
Baseline	DM poorly controlled	Φ	Random	0.14	[-0.23<>0.51]	0.46	89%	<0.00001	S7.28
	Europe	12	Random	-0.01	[-0.22<>0.20]	0.93	94%	<0.00001	S7.40
	Asia	12	Random	0.46	[0.27<>0.64]	<0.00001	53%	0.02	S7.43
	South America	Φ	Random	0.28	[-0.11<>0.67]	91.0	%06	<0.00001	S7.46
	Overall	32	Random	0.16	[0.03<>0.29]	0.01	94%	<0.00001	87.2
	PPD >7mm	4	Fixed	1.21	[-0.25<>2.67]	0.0	88%	<0.0001	S7.38
	DM well controlled	14	Random	0.15	[0.03<>0.26]	0.01	49%	0.02	S7.26
End	DM poorly controlled	ω	Random	0.15	[-0.01<>0.32]	0.07	51%	0.05	S7.29
	Europe	12	Random	0.03	[-0.17<>0.23]	0.76	97%	<0.00001	S7.41
	Asia	12	Random	0.28	[0.11<>0.45]	0.001	%99	0.0007	S7.44
	South America	∞	Random	0.20	[0.04<>0.37]	0.02	53%	0.04	S7.47

	Overall	21	Random	0.02	[0.06<>0.10]	0.57	88%	<0.00001	S7.3
	PPD >7mm	m	Fixed	0.34	[-0.94<>>1.62]	09:0	73%	0.03	87.39
	DM well controlled	7	Random	0.03	[-0.07<>0.14]	0.54	76%	0.00003	S7.27
Differen	DM poorly controlled	O.	Random	0.07	[-0.06<>0.21]	0.29	75%	0.003	87.30
oe	Europe	80	Random	0.08	[0.01<>>0.16]	0.03	47%	0.003	S7.42
	Asia	9	Random	0.13	[-0.11<>>0.37]	0.28	%98	<0.00001	S7.45
	South America	7	Random	-0.18	[-0.34<>>-0.03]	0.02	77%	0.0002	S7.48

	Table 3B CAL								
	Measurement moment	Included studies #	Mode	DiffM (mm)	Test overall	verall	Test for he	Test for heterogeneity	For details see Figure/Appendix
		comparisons			95% CI	p-value	P value (%)	p-value	
	Overall	72	Random	0.27	[0.13<>0.41]	0.0001	83%	<0.00001	87.4
	DM well controlled	12	Random	0.23	[0.08<>0.38]	0.003	54%	0.01	S7.31
	DM poorly controlled	ο	Random	0.14	[-0.09<>0.38]	0.24	40%	LL.O	S7.34
Baseline	Europe	12	Random	0.22	[-0.02<>0.45]	0.07	%06	<0.00001	S7.49
	Asia	7	Random	0.25	[0.05<>0.46]	0.02	71%	0.002	S7.52
	South America	80	Random	0.41	[0.08<>0.74]	10.0	%19	0.01	87.55
	Overall	27	Random	0.26	[0.05<>0.47]	0.02	%96	<0.00001	S7.5
	DM well controlled	12	Random	0.22	[0.07<>0.37]	0.003	58%	900.0	S7.32
End	DM poorly controlled	Φ	Random	0.20	[-0.01<>0.42]	0.07	18%	0.29	S7.35
	Europe	12	Random	0.24	[-0.14<>0.62]	0.21	%86	<0.00001	87.50
	Asia	7	Random	0.21	[-0.00<>0.42]	0.05	76%	0.0003	S7.53
	South America	80	Random	0.32	[0.05<>0.60]	0.02	52%	0.04	S7.56
	Overall	18	Random	-0.06	[-0.19<>0.07]	0.38	94%	<0.00001	87.6
Diffe	DM well controlled	9	Random	90:0	[-0.04<>0.16]	0.25	45%	01.0	S7.33
erence	DM poorly controlled	5	Random	0.08	[0.02<>0.14]	0.01	17%	0:30	S7.36
	Europe	Φ	Random	-0.02	[0.23<>0.19]	98.0	%16	<0.00001	S7.51
	Asia	ო	Fixed	-0.02	[-0.13<>0.09]	0.72	82%	0.004	S7.54
	South America	7	Random	-0.13	[-0.32<>0.05]	71.0	73%	0.001	S7.57

	Table 3C-I BOP %								
	Measurement moment	Included studies#	Model	DiffM (mm)	Testo	Test overall	Test for he	Test for heterogeneity	For details see Figure/Appendix
		comparisons			10 %56	b-value	l² value (%)	b-value	
Baseline	Overall	14	Random	0.38	[-8.01<>8.77]	0.93	%96	<0.00001	87.10
End	Overall	14	Random	4.64	[1.39<>7.89]	0.005	97%	<0.00001	87.11
Difference	Overall	53	Random	4.39	[-3.91<>12.71]	0:30	000%	<0.00001	S7.12

	Table 3C-II GBI - Ainamo & Bay (1975)	ley (1975)							
	Measurement moment	Included studies #	Model	DiffM (mm)	Test overall	werall	Test for he	Test for heterogeneity	For details see Figure/Appendix
		comparisons			IO %56	b-value	l² value (%)	p-value	
Baseline	Overall	٥	Random	1.81	[-4.03<>7.64]	0.54	54%	0.03	87.13
End	Overall	٥	Random	1.57	[-0.05<>3.18]	90.0	%99	0.003	S7.14
Difference	Overall	4	Random	-17.94	[-40.62<>4.73]	0.12	%96	<0.00001	S7.15

	Table 3D Gingival index - Loë & Silness (1963)	ë & Silness (1963)							
	Measurement moment	Included studies#	Model	DiffM (mm)	Testo	Testoverall	Test for he	Test for heterogeneity	For details see Figure/Appendix
		comparisons			IO %56	p-value	l² value (%)	p-value	
Baseline	Overall	71	Random	0.13	[0.05<>0.22]	0.003	57%	0.002	87.7
End	Overall	71	Random	0.18	[0.10<>0.25]	<0.00001	84%	<0.00001	87.8
Difference	Overall	7	Random	0.01	[0.01<>0.13]	0.86	9%65	0.02	87.9

	Table 3E-I Plaque scores %								
	Measurement moment	Included studies#	Model	DiffM (mm)	Test overall	werall	Testforhe	Test for heterogeneity	For details see Figure/Appendix
		comparisons			IO %56	p-value	I² value (%)	b-value	
Baseline	Overall	71	Random	3.69	[-3.88<>11.25]	0.34	95%	<0.00001	87.19
End	Overall	7.	Random	-0.48	[-7.65<>6.70]	0.90	%96	<0.00001	87.20
Difference	Overall	4	Random	-2.80	[6.47<>0.87]	0.14	83%	<0.00001	S7.21

	For details see Figure/Appendix		S7.22
	Test for heterogeneity	p-value	<0.00001
	Test for he	l² value (%)	77%
	verall	p-value	0.59
	Testoverall	10 %56	-0.09<>0.16
	DiffM (mm)		0.03
	Model		Random
ë (1964)	Included studies#	comparisons	91
Table 3E-II PI – Silness en Loë (1964)	Measurement moment		Overall
			Baseline

S7.23	S7.24
<0.00001	<0.00001
92%	94%
0.29	0.28
-0.06<>0.19	-0.80<>0.23
0.07	-0.28
Random	Random
35	4
Overall	Overall
End	Difference

	Table 3F Gingival recession (REC)	(REC)							
	Measurement moment	Included studies #	Model	DiffM (mm)	Testoverall	verall	Test for he	Test for heterogeneity	For details see Figure/Appendix
		comparisons			10 %56	p-value	l² value (%)	p-value	
Baseline	Overall	4	Random	0.22	[-0.1]<>0.56]	0.18	11%	0.34	57.16
End	Overall	4	Random	0.05	[-0.49<>0.60]	0.85	%89	0.02	S7.77
Difference	Overall	m	Fixed	-0.10	[-0.27<>0.06]	0.23	%0	0.67	S7.18

Significant	Meta-analyses outcomes: p<0.05	
Not significant	Meta-analyses outcomes: p≥0.05	
Significance	(d)	

Meta-analyses outcomes resulting in a p<0.05 was considered to be statistically significant. $^{\text{l}_3}$

ial Considerable	75-100%
Substantia	%06-09
Moderate	30-60%
Potential not important	0–40%
Test of heterogeneity	(12)

As a guideline, to assess the potential magnitude of inconsistency between studies, an P statistic of 0%-40% may represent unimportant levels of heterogeneity, 30%-90% may represent substantial heterogeneity. An P statistic of greater than 75% was interpreted to indicate considerable heterogeneity.

Sub-analysis

The sub-analysis regarding the regulation of DM revealed a significant difference in favor of non-DM compared to controlled DM for PPD before (DiffM=0.23, p=0.01, 95% CI 0.05<>0.42) and after treatment (DiffM=0.15, p=0.01, 95% CI 0.03<>0.26). Also, for CAL significant differences were in favor of non-DM at baseline (DiffM=0.23, p=0.003, 95%CI 0.08<>0.38) and after treatment (DiffM=0.22, p=0.003, 95% CI 0.07<>0.37). For uncontrolled DM significant findings were found for CAL concerning the incremental data (DiffM=0.08, p=0.01, 95% CI 0.02<>0.14) and estimated to be a 'zero' effect³ (Table 3A+B and Online Appendix S7). Sub-analysis for PPD \geq 7mm showed no significant difference in treatment response between the groups (Table 3A, Online Appendix S7.39). Based on a sub-analysis of geographical regions in which the study was performed, significant findings were found for PPD reduction in Europe (DiffM=0.08, p=0.03, 95% CI 0.01<>0.16) in favor of non-DM but estimated to be a 'zero' effect.³ In contrast, significant findings were found for PPD in favor of DM in South America (DiffM=-0.18, p=0.02, 95% CI -0.34<>0.03) but also estimated to be a 'zero' effect.³ For CAL, the data revealed no overall statistical differences between the groups across different geographical regions (Table 3A+B, Online Appendix S7).

Statistical heterogeneity

The funnel plot (Online Appendix S8) shows that almost all outcomes are located at the top of the funnel, which is suggestive for publication bias. Egger's test shows a non-significant p-value for the primary outcomes (p=0.2771, p=0.4690). Statistically, heterogeneity was tested and was significant for all performed meta-analyses, except for data concerning REC and sub-analysis for DM regulation on CAL (Table 3).

Evidence profile

Table 4 presents a summary of the factors employed to establish the body of evidence profile according to the GRADE⁵⁰ framework relative to the magnitude of the risk.

The 30 observational studies examined (portrayed in Figure 1) demonstrated that the potential risk of bias was estimated to be 'low' to 'critical' (Online Appendix S3). Data from the included studies were derived from different populations and continents. Therefore, these findings are considered to be 'generalizable'. Based on the heterogeneity between the included studies, data were judged to be 'rather inconsistent' (presented in Table 3). The data were considered to be 'rather precise' because all selected studies focused on NSPT as a primary outcome and because the majority revealed an overlap in the overall 95% CI (Table 3, Online Appendix S7). As publication bias may have been present, the presence of reporting bias is likely. Considering all GRADE aspects, the evidence profile that emerges from this review is that the strength of the evidence is 'moderate'. Based on a synthesis of this evidence, there is moderate certainty that patients with DM and periodontitis have comparable treatment outcomes to non-DM when undergoing NSPT.

Summary of findings table of the quality and body of evidence and appraisal of the strength and the estimated evidence profile and of the outcome regarding NSPT Table 4

	Primary	Primary outcomes		Secondary outcomes	(0)
Determinants of the Quality	DPD	CAL	Bleeding indices	Plaque indices	REC
Study design			Observational studies	ies	
included studies			30		
#comparisons	32	27	40	32	4
Risk of bias (Online Appendix S3)	Low to critical	Low to critical	Low to critical	Low to critical	Moderate to serious
Consistency (Table 5)	Rather consistent	Rather consistent	Rather consistent	Rather consistent	Rather consistent
Directness (Table 2)	Generalizable	Generalizable	Generalizable	Generalizable	Generalizable
Precision (Figure 2+3, Table 5, Online Appendix S4)	Rather precise	Rather precise	Rather precise	Rather precise	Rather precise
Reporting bias (Online Appendix S5)	Likely	Likely	Likely	Likely	Likely
Strength based on the quality and body of evidence	Moderate	Moderate	Moderate	Moderate	Moderate
Summary and direction of the findings	There is a moderate DM with comparable	rate certainty that patients with DM undergorable outcomes for periodontal parameters.	with DM undergoing N ntal parameters.	There is a moderate certainty that patients with DM undergoing NSPT can be treated as effectively as non- DM with comparable outcomes for periodontal parameters.	ffectively as non-

DISCUSSION

Summary of findings

The present review summarized and synthesized the available literature for the response to treatment of DM periodontitis patients undergoing NSPT. The majority of the 30 included studies demonstrated significant improvements in periodontal parameters following NSPT for both DM and non-DM (see Online Appendix S6). This is consistent with the findings of a recent SR, which reported that NSPT is effective for infection control in periodontitis patients. However, the present analysis observed no clinically relevant difference in treatment response between the DM and non-DM periodontitis patients. The finding should be interpreted with some caution considering the statistical heterogeneity, limitations and potential biases in the data that emerged from the included studies. On the other hand, the TSA demonstrates that additional data are unlikely to alter the summary effect.

As prediabetes may be reversible,85 data regarding this condition were excluded. Gestational diabetes consists of high blood glucose only during pregnancy86 and was consequently not analyzed in the present SR.

The association between DM and periodontal therapy

Previous 'in vitro' and 'in vivo' studies, both in animals and humans, have established a relationship between DM and periodontitis. Supposedly the host response to bacterial challenge does differ in patients with DM involving aspects of immune functioning, neutrophil activity and cytokine biology. Moreover, the accumulation of reactive oxygenspecies, oxidative stress, and interactions between advanced glycation end AGEs in the periodontal tissues and their receptor contribute to increased inflammation in the periodontal tissues in people with DM. It might therefore be presumed that DM patients exhibit a reduced response to therapy as compared to non-DM individuals. However, the nature of the bacterial challenge in patients with DM and periodontitis does not seem to differ from that of non-DM. PDD and CAL in adults with type I/II DM. This is consistent with the present comprehensive synthesis which indicates that periodontitis patients with DM receiving NSPT can achieve similar clinical results after they have undergone NSPT compared to non-DM, challenging the more assertive claims made in previous studies.

Primary outcomes

The baseline DiffM values were significantly different for CAL and PPD between DM and non-DM (0.27 and 0.21 mm, respectively – see Table 3A+B). Baseline differences might indicate the presence of confounders responsible for differences in outcomes. In the present analysis, the difference in DiffM was skewed towards the DM group. This could be attributed to confounding factors such as impaired glycemic control, altered inflammatory response, and compromised immune function in diabetic individuals, which may predispose them to a more severe form of periodontal disease. Such differences in baseline scores can affect the validity and reliability of a study. If groups being compared start with different baselines, it becomes challenging to attribute observed differences at follow-up to the intervention or treatment being tested rather than to pre-existing differences. However, the end DiffM values were also significantly different for CAL and PPD between DM and non-DM to more or less the same extent (0.26 and 0.16 mm, respectively – see Table 3A+B). Consequently, the incremental DiffM indicating the treatment effect was very small (0.06 and 0.02 mm, respectively – see Table 3A+B) and not significantly different. The extent of this difference in treatment effect with CAL can be

interpreted as a 'zero-effect'.³⁶ Smiley et al.³⁶ unfortunately do not provide guidelines for the interpretation of changes in PPD. However, as changes in PPD encompass both changes in CAL and the location of the gingival margin, it is reasonable to assume that changes in PPD should be at least as large as changes in CAL and presumably larger. Given that the DiffM of the incremental difference for PPD was 0.02 mm while it was 0.06 mm for CAL, one can safely interpret the difference in treatment effect between DM and non-DM as also being a 'zero-effect'.

Secondary outcomes

Analysis of the plaque indices (Table 3E I+II) shows that there was no difference between groups, indicating that the level of oral hygiene was comparable for DM and non-DM. Similar to the PPD and CAL scores, the GI scores at baseline and end-trial were also significantly different. However, the change in GI as a result of treatment was such that no significant difference was observed in the incremental difference between scores (see Table 3D). This also suggests that there is no difference in treatment response between DM and non-DM, although one may argue whether the GI is an appropriate index concerning periodontitis. The Gl is based on both visual signs of inflammation and bleeding on probing, with an emphasis on visual signs. It may therefore not capture the severity of periodontitis accurately, because, in the case of thick gingiva, the inflammatory infiltrate is not visible from the oral aspect. 95,96 Studies have shown that for an objective diagnosis of the presence of an inflammatory lesion, the determination of BOP is a more reliable method.% The present analysis shows no significant DiffM in the incremental difference between baseline and end-trial BOP scores (see Table 3C I+II). Additionally, the remaining meta-analyses of REC did not reveal any statistical differences (p<0.05), reinforcing that DM did not affect the response to periodontal treatment (see Table 3E).

Trial sequential analysis

TSA is valuable in SRs because it helps maintain the reliability and validity of conclusions drawn from meta-analyses by controlling for random errors and adjusting for the risk of false positives and negatives. It is a cumulative random-effects meta-analysis method that estimates a "required information size" (i.e. required meta-analysis sample size) using the same framework as sample size calculations for individual studies, while also accounting for heterogeneity and multiple comparisons when new studies are added. This ensures that the cumulative evidence is sufficiently robust before confirming or refuting the effectiveness, thus preventing premature conclusions and improving the overall quality of the evidence synthesis in meta-analysis. Based on the TSA of these meta-analyses, the effect was found to be conclusive and reliable suggesting that the evidence of these meta-analyses is firm, indicating that additional data are unlikely to alter the summary effect (for details see Figure 2A+B).

Sub-analysis for uncontrolled and controlled DM

The differentiation between well-controlled and poorly controlled DM in the primary studies was mainly done by self-report (questionnaires) or clinical assessment using HbA1c levels. This distinction is important, as self-reported data can be subject to recall bias and inaccuracies, potentially leading to misclassification of DM control status. In contrast, HbA1c levels provide a more objective and reliable measure of long-term blood glucose control. When the regulation of DM was not differentiated, reported HbA1c levels were used to categorize the DM population for analysis. This could ensure a clearer distinction between the groups, providing a more accurate representation of each group.

Data from a USA National Health and Nutrition Examination Survey show a higher likelihood of periodontitis in patients with poorly controlled DM compared to non-DM individuals. Moreover, it has been shown that poorly controlled DM is associated with more severe periodontal disease. Sub-analysis regarding DM regulation on the primary outcomes found no significant DiffM in the incremental data for well-controlled DM compared to non-DM. However, for uncontrolled DM patients, a significant DiffM was observed for the incremental scores regarding CAL (DiffM=0.08, p=0.01). Despite this, if the corresponding DiffM is interpreted according to Smiley et al., the effect is estimated as 'zero'. Consequently, DM regulation appears to have no clinical effect on the response to NSPT (For details see Table 3A+B, Online Appendix S7.25–S7.36).

Type of DM

DM type I typically develops during childhood or adolescence, although it can also occur in adults. In contrast, type II often develops later in life and is more common in adults, accounting for approximately 90% of all DM cases. Additionally, it is important to note that periodontitis is more prevalent in older people. DM Therefore, only patients aged 18 and above were included in this study. Out of the 30 included papers, 26 studies specifically focused on DM type II so the results may primarily reflect the effectiveness of NSPT in this population. Only three studies focused on DM type IS5.65,73, but two did not provide an SD or SE. Therefore, it was not possible to perform a subgroup analysis to compare types I and II DM data. In the descriptive analysis (see Online Appendix S5.1), none of the type I DM studies identified a significant difference compared to non-DM for PPD. Furthermore, a recent evidence review has summarized that NSPT was effective in both type I and II. However, this study compared NSPT to usual care and did not include a control group. While it is plausible that periodontal therapy is also effective in patients with DM type I and this SR may have limitations in its generalizability, the broader evidence supports the effectiveness of NSPT across both types of DM.

Smoking

Smoking is a well-established risk factor for both periodontitis and DM increasing periodontal tissue loss and presumably complicating the treatment of DM.^{22,94,101} Moreover, smoking impairs periodontal treatment outcomes.¹⁰¹ The majority of the studies excluded smokers with only five also enrolled smokers.^{51,57,61,66,67} These did however not provide separate treatment outcomes for smokers and non-smokers. Therefore, it was not possible to evaluate the potential impact of smoking on NSPT outcomes.

Adjunctive antibiotics

Adjunctive antibiotics have been used to improve clinical outcomes of NSPT.¹⁰² It is reported that the adjunctive use of antibiotics may have limited benefit for periodontal treatment outcomes in patients with DM.¹⁰³ In the present review, the effect of antibiotics on treatment outcomes in DM subjects could not be determined because none of the included studies included the systemic use of antibiotics. In one included study⁷³ amoxicillin as antibiotic prophylaxis 1h before the appointment was prescribed for DM patients.

Limitations

Factors such as differentiation between DM types I and II, smoking habits and various examination protocols may have influenced the heterogeneity. These could not be further analyzed due to a lack of complete descriptions of the population included in the original studies. Moreover, the language restriction to English resulted in one potential study that was excluded (see Online Appendix S1).

CONCLUSION

Although there was a significant DiffM for the primary outcomes between DM and non-DM groups at baseline, a similar difference was observed in the end data. This indicates that the treatment effect between the two groups was not significantly different, as is evident from the DiffM of the incremental data for CAL and PPD. Therefore, the overall evidence from this systematic review indicates that there is no statistically significant difference in treatment outcomes between periodontitis patients with DM and non-DM. Based on the evidence profile, it can be stated with moderate certainty that the difference in treatment outcomes following NSPT between periodontitis patients with DM and non-DM is insignificant.

CLINICAL RELEVANCE

Scientific rationale for this analysis

Evidence supports an increased risk for periodontal diseases in DM patients. This may potentially influence the response to periodontal therapy. This SR aimed to evaluate the impact of DM on treatment outcomes following NSPT.

Principle findings

In periodontitis patients the treatment outcomes following NSPT did not show a significant difference between patients with or without DM.

Practical implications

Periodontitis patients with DM can be treated as effectively as non-DM periodontitis patients when undergoing NSPT.

Online Appendices



STATEMENTS

Acknowledgements

The authors acknowledge Joost Bouwman, head librarian of the Academic Centre for Dentistry Amsterdam, for his help in retrieving the full-text articles. In addition, L. Žiūkaitė for her contribution on this topic. The authors acknowledge the following authors for their responses, time and effort searching for additional data: prof. Dr. Tervonen, prof. N.J. López, prof. Dr. Cirano, Prof. Dr. M. Christgau, Prof. Dr. G. Camargo, Prof. Dr. Orrico, prof. M. Holzhasen, prof. F.O. Corea, prof. C.S. Boghossian, prof. J. Mirnic, drs. A. Kudva, prof. R. Almeida, prof. N. Budeneli, prof. A.P. Kolte and prof. B.C.V. Gurgel.

Statement of ethics

This study is registered at the International Prospective Register of Systematic Reviews (PROSPERO) by number CRD42021227543 and approved by the ACTA Institutional Review Board, by reference number 2022-43514.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This SR was self-funded by the authors and their respective institutions as work for this paper is funded by a regular academic appointment at the Academic Center for Dentistry Amsterdam (ACTA) of Slot, Thomassen, Van der Weijden and Weijdijk.

Data statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Author contributions

LPMW: contributed to conception and design, search and selection, analysis and interpretation, and drafted the manuscript.

TMJAT: contributed to selection, analysis and interpretation and critically revised the manuscript.

NCK: contributed to contributed to selection, analysis and interpretation of the data.

EEJM: contributed to analysis and critically revised the manuscript.

CV: contributed to analysis and critically revised the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

REFERENCES

The papers included in this synthesis are highlighted in **bold** in the list.

- 1. Könönen E, Gursoy M, Gursoy UK. Periodontitis: a multifaceted disease of tooth-supporting tissues. *J Clin Med.* 2019;8(8):1135.
- 2. Kassebaum NJ, Smith AGC, Bernabé E, et al. Global, regional, and national prevalence, incidence, and disability adjusted life years for oral conditions for 195 countries, 1990–2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. *J Dent Res.* 2017;96(4):380–387.
- 3. Ramseier CA, Anerud A, Dulac M, et al. Natural history of periodontitis: Disease progression and tooth loss over 40 years. *J Clin Periodontol*. 2017;44(12):1182-1191.
- 4. Abdulkareem AA, Al-Taweel FB, Al-Sharqi AJB, Gul SS, Sha A, Chapple ILC. Current concepts in the pathogenesis of periodontitis: from symbiosis to dysbiosis. *J Oral Microbiol*. 2023;15(1). doi:10.1080/20002297.2023.2197779
- 5. Teeuw WJ, Gerdes VE, Loos B. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. *Diabetes Care*. 2010;33(2):421-427.
- 6. Chapple I, Mealey B, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontal*. 2018;89:S74-S84.
- 7. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. . *J Dent Res.* 2014;93(11):1045-1053.
- 8. Chapple IL, Genco R. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol.* 2013;84(4-s):S106-S112. doi:10.1902/JOP.2013.1340011
- 9. Chávarry NGM, Vettore MV, Sansone C, Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. *Oral Health Prev Dent.* 2009;7(2):107-127.
- 10. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. *J Diabetes Complications*. 2006;20(1):59-68. doi:10.1016/j.jdiacomp.2005.05.006
- 11. Ziukaite L, Slot DE, Van der Weijden FA. Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies. *J Clin Periodontol.* Published online 2018. doi:10.1111/jcpe.12839
- 12. Păunică I, Giurgiu M, Dumitriu AS, et al. The Bidirectional Relationship between Periodontal Disease and Diabetes Mellitus-A Review. *Diagnostics (Basel)*. 2023;13(4):681.
- 13. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103(2):137-149. doi:10.1016/J.DIABRES.2013.11.002
- 14. Di Domenico GL, Minoli M, Discepoli N, Ambrosi A, de Sanctis M. Effectiveness of periodontal treatment to improve glycemic control: an umbrella review. *Acta Diabetol.* 2023;60(1):101-113.
- 15. Hsu YT, Nair M, Angelov N, Lalla E, Lee CT. Impact of diabetes on clinical periodontal outcomes following non-surgical periodontal therapy. *J Clin Periodontol.* 2019;46(2):206-217.
- 16. Lang NP, Joss A, Orsanic T, Gusberti FA, Siegrist BE. A predictor for the progression of periodontal disease? *J Clin Periodontal*. 1986;13(6):590-600.
- 17. Lang, NP, Bartold PM. Periodontal health. Journal of periodontology. 2018;89: S9-S16.
- 18. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (Updated August 2023). 2nd ed. John Wiley & Sons, 2019; 2023. doi:10.1002/9780470712184
- 19. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012.
- 20. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;2(349):g7647.
- 21. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int.* 2018;121 (Pt1):1027-1031. doi:10.1016/j.envint.2018.07.015
- 22. Preshaw PM, Alba AL, Herrera D, et al. Periodontitis and diabetes: A two-way relationship. *Diabetologia*. 2012;55(1):21-31. doi:10.1007/s00125-011-2342-y
- 23. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Systematic Reviews. doi:10.1186/s13643-016-0384-4
- 24. Moola S, Munn Z, Tufanaru C, et al. Critical Appraisal Checklist for Analytical Cross Sectional Studies. In: Aromataris E, Munn Z, eds. Chapter 7: The Joanna Briggs Institute; 2017. https://reviewersmanual.joannabriggs.org/
- 25. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2012.
- 26. Higgins JPT, Morgan RL, Rooney AA, et al. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). *Environment International 2024*. doi:10.1016/j.envint.2024.108602
- 27. van der Weijden FN, Kuitert RB, Berkhout FRU, van der Weijden GA. Influence of tooth position on wind

- instrumentalists' performance and embouchure comfort: A systematic review. *Journal of Orofacial Orthopedics*. 2018;79(3):205-218. doi:10.1007/s00056-018-0128-2
- 28. MA Listgarten. Periodontal probing: what does it mean? J Clin Periodontol. 1980;7(3):165-176.
- 29. Highfield J. Diagnosis and classification of periodontal disease. Aust Dent J. 2009;54(1):11-26.
- 30. Ainamo J, Bay I. Problems and proposals for recording gingivitis and plaque. Int Dent J. 1975;25(4):229-235.
- 31. Löe H. The Gingival Index, the Plaque Index and the Retention Index Systems. J Periodontol. 1967;38(6):610-616.
- 32. O'Leary TJ, Drake RB, Naylor JE. The plaque control record. J Periodontol. 1972;43(1):38.
- 33. Silness J, Loe H. Periodontal Disease in Pregnancy. II. Correlation between Oral Hygiene and Periodontal Condition. *Acta Odontol Scand.* 1964;22:121-135.
- 34. Goldman HM, Cohen DW. Periodontal therapy. The CV Mosby Company, St Louis. Published online 1968:80-82.
- 35. Newman MG, Takei H, Klokkeveld PR, Carranza FA, editors. Carranza's Clinical Periodontology. Elsevier; 2014.
- 36. Smiley CJ, Tracy SL, Abt E, et al. Evidence-based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. *Journal of the American Dental Association*, 2015;146(7):525–535, doi:10.1016/j.adaj.2015.01.026
- 37. The Nordic Cochrane Centre. Review Manager (RevMan). Cochrane Collaboration. Published online 2024. revman. cochrane.org.
- 38. Egger Matthias, Smith George Davey, Schneider Martin, Minder Christoph. Bias in meta-analysis detected by a simple, graphical test. *Br Med J.* 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
- 39. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. J Am Med Assoc. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008
- 40. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA GROUP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 2009;6(7):e1000097. doi:10.14306/renhyd.18.3.114
- 41. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med. 1994;13:1341-1352.
- 42. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549.
- 43. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol.* 2008;61:64-75.
- 44. Thorlund K, Engstrøm J, Wetterslev J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). Copenhagen Trial Unit, 2011. Copenhagen, Denmark: Centre for Clinical Intervention Research. Published online 2017:1-119.
- 45. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive—Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol. 2009;38:287-298.
- 46. Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clin Epidemiol. 2010;2:57-66.
- 47. Roshanov PS, Dennis BB, Pasic N, Garg AX, Walsh M. When is a meta-analysis conclusive? A guide to Trial Sequential Analysis with an example of remote ischemic preconditioning for renoprotection in patients undergoing cardiac surgery. *Nephrol Dialvsis Transplant*. 2017;32:ii33-ii30.
- 48. Ryan R, Cochrane Consumers and Communication Review Group. Heterogeneity and Subgroup Analyses in Cochrane Consumers and Communication Group Reviews: Planning the Analysis at Protocol Stage.; 2016. https://cccrg.cochrane.org/
- 49. Meader N, King K, Llewellyn A, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: Development and pilot validation. Syst Rev. 2014;24(3):82. doi:10.1186/2046-4053-3-82
- 50. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol. 2013;66(2):151-157. doi:10.1016/j.jclinepi.2012.01.006
- 51. Navarro-Sanchez AB, Faria-Almeida R, Bascones-Martinez A. Effect of non-surgical periodontal therapy on clinical and immunological response and glycaemic control in type 2 diabetic patients with moderate periodontitis. *J Clin Periodontol.* 2007;34(10):835-843. doi:10.1111/j.1600-051X.2007.01127.x
- 52. Faria-Almeida R, Navarro A, Bascones A. Clinical and Metabolic Changes After Conventional Treatment of Type 2 Diabetic Patients With Chronic Periodontitis. *J Periodontol.* 2006;77(4):591-598. doi:10.1902/jop.2006.050084
- 53. Gonçalves D. The effect of non-surgical periodontal therapy on peroxidase activity in diabetic patients: a case-control pilot study. *J Clin Periodontol*. 2008;35:799-806. doi:10.1111/j.1600
- 54. Silva-Boghossian CM, Orrico SRP, Gonçalves D, Correa FOB, Colombo APV. Microbiological changes after periodontal therapy in diabetic patients with inadequate metabolic control. *Braz Oral Res.* 2014;28(1). doi:10.1590/1807-3107bor-2014.vol28.0007
- 55. Tervonen Tellervo, Karjalainen Kaisa. Periodontal disease related to diabetic status. *J Clin Periodontol.* 1997;24(7):505-510.
- 56. Tervonen Tellervo, Knuuttila Matti, Pohjamo Leena, Nurkkala Helena. Immediate response to non-surgical periodontal treatment in subjects with diabetes mellitus. *J Clin Periodontol*. 1991;18(1):65-68.
- 57. Christgau M, Palitzsch K-D, Sclimah G, Kreiner U, Frenzel S. Periodontal therapy in diabetics. *journal of Clinical periodontology*. 1998;25:112-124.

- 58. Sonoki K, Nakashima S, Takata Y, et al. Decreased Lipid Peroxidation Following Periodontal Therapy in Type 2 Diabetic Patients. *J Periodontol.* 2006;77(11):1907-1913. doi:10.1902/jop.2006.060088
- 59. Correa FOB, Gonçalves D, Figueredo CMS, Gustafsson A, Orrico SRP. The Short-Term Effectiveness of Non-Surgical Treatment in Reducing Levels of Interleukin-1β and Proteases in Gingival Crevicular Fluid From Patients With Type 2 Diabetes Mellitus and Chronic Periodontitis. *J Periodontol.* 2008;79(11):2143-2150. doi:10.1902/jop.2008.080132
- 60. Dağ A, Firat ET, Arikan Ş, Kadiroğlu AK, Kaplan A. The effect of periodontal therapy on serum TNF-α and HbA1c levels in type 2 diabetic patients. *Aust Dent J.* 2009;54(1):17-22. doi:10.1111/j.1834-7819.2008.01083.x
- 61. Kardeşler L, Buduneli N, Çetinkalp Ş, Kinane DF. Adipokines and Inflammatory Mediators After Initial Periodontal Treatment in Patients With Type 2 Diabetes and Chronic Periodontitis. *J Periodontol.* 2010;81(1):24-33. doi:10.1902/jop.2009.090267
- 62. Kudva P, Tabasum S, Garg N. Evaluation of clinical and metabolic changes after non surgical periodontal treatment of type 2 diabetes mellitus patients: A clinico biochemical study. *J Indian Soc Periodontol.* 2010;14(4):257. doi:10.4103/0972-124x.76933
- 63. Hungund S, Panseriya BJ. Reduction in HbA1c levels following non-surgical periodontal therapy in type-2 diabetic patients with chronic generalized periodontitis: A periodontist's role. *J Indian Soc Periodontol.* 2012;16(1):16-21. doi:10.4103/0972-124X.94598
- 64. Fabiano Ribeiro Cirano, Claudia Pêra, Paulo Ueda, et al. Clinical and metabolic evaluation of one-stage, full-mouth, ultrasonic debridement as a therapeutic approach for uncontrolled type 2 diabetic patients with periodontitis. *Quintessence Int (Berl)*. 2012;43(8):671-681.
- 65. Buzinin SM, Alabsi AM, Tan ATB, Vincent-Chong VK, Swaminathan D. Effects of nonsurgical periodontal therapy on clinical response, microbiological profile, and glycemic control in Malaysian subjects with type 1 diabetes. *Scientific World Journal*. 2014;2014:232535. doi:10.1155/2014/232535
- 66. López NJ, Quintero A, Casanova PA, Martínez B. Routine Prophylaxes Every 3 Months Improves Chronic Periodontitis Status in Type 2 Diabetes. *J Periodontol.* 2014;85(7):e232-e240. doi:10.1902/jop.2013.130400
- 67. Kara G, Cifcibasi E, Karsidag K, Cintan S. Short term effects of periodontal therapy on inflammatory markers in patients with type-2 diabetes. *Saudi Med J.* 2015;36(4):469-476. doi:10.15537/smj.2015.4.10380
- 68. Kaur PK, Narula SC, Rajput R, Sharma RK, Tewari S. Periodontal and glycemic effects of nonsurgical periodontal therapy in patients with type 2 diabetes stratified by baseline HbA1c. *J Oral Sci.* 2015;57(3):201-211. doi:10.2334/josnusd.57.201
- 69. Pannicker JJ, Mehta DS. Effects of scaling and root planing on gingival crevicular fluid vascular endothelial growth factor level in chronic periodontitis patients with and without diabetes mellitus: A clinicobiochemical study. *J Indian Soc Periodontol.* 2016;20(3):244-248. doi:10.4103/0972-124X.176395
- 70. Doğan ŞB, Ballı U, Dede FÖ, Sertoğlu E, Tazegül K. Chemerin as a Novel Crevicular Fluid Marker of Patients With Periodontitis and Type 2 Diabetes Mellitus. *J Periodontol.* 2016;87(8):923-933. doi:10.1902/jop.2016.150657
- 71. Mishra V, Shettar L, Bajaj M, Math AS, Thakur SL. Interlinking periodontitis and type 2 diabetes mellitus by assessment of crevicular visfatin levels in health and in disease before and after initial periodontal therapy. *Journal of Clinical and Diagnostic Research*. 2016;10(8):ZC67-ZC71. doi:10.7860/JCDR/2016/18656.8283
- 72. Abreu IS, Euzebio Alves VT, Benedete APS, et al. Gingival crevicular fluid levels of protease-activated receptors type 1 and type 2 in diabetic patients with periodontitis. *J Periodontal Res.* 2016;51(5):577-585. doi:10.1111/jre.12336
- 73. Peruzzo Lopes CC, do Monte Ribeiro Busato P, Michelin Mânica MF, et al. Effect of basic periodontal treatment on glycemic control and inflammation in patients with diabetes mellitus type 1 and type 2: controlled clinical trial. *Journal of Public Health (Germany)*. 2017;25(4):443-449. doi:10.1007/s10389-017-0792-5
- 74. Sundaram G, Ramakrishnan T, Parthasarathy H, Moses J, Lalitha T. Evaluation of micronutrient (Zinc, Magnesium, and Copper) levels in serum and glycemic status after nonsurgical periodontal therapy in type 2 diabetic patients with chronic periodontitis. *Contemp Clin Dent.* 2017;8(1):26-32. doi:10.4103/0976-237X.205036
- 75. Gayathri S, Koshi E, Sadasivan A, Arunima PR, Jaya Kumar K. Effect of initial periodontal therapy on serum nitric oxide levels in chronic periodontitis patients with or without type 2 diabetes mellitus. *Journal of Contemporary Dental Practice*. 2019;20(2):197-203. doi:10.5005/jp-journals-10024-2497
- 76. Ahuja CR, Kolte AP, Kolte RA, Gupta M, Chari S. Effect of non-surgical periodontal treatment on gingival crevicular fluid and serum leptin levels in periodontally healthy chronic periodontitis and chronic periodontitis patients with type 2 diabetes mellitus. *J Investig Clin Dent.* 2019;10(3). doi:10.1111/jicd.12420
- 77. Pragada L, Mehta DS, Manasa V, Bathini CG, Kesari S, Bansal R. Effect of scaling and root planing on gingival crevicular fluid levels of adrenomedullin in chronic periodontitis patients with and without diabetes mellitus type 2: A clinico-biochemical study. *Ann Afr Med.* 2019;18(2):92-96. doi:10.4103/aam.aam_40_18
- 78. Almeida ML, Duarte PM, Figueira EA, et al. Effects of a full-mouth disinfection protocol on the treatment of type-2 diabetic and non-diabetic subjects with mild-to-moderate periodontitis: one-year clinical outcomes. *Clin Oral Investig.* 2020;24(1):333-341. doi:10.1007/s00784-019-02927-8
- 79. Mirnić J, Đurić M, Nikolić N, et al. Clinical and Microbiological Assessment of Non-Surgical Treatment of Chronic Periodontitis in Controlled and Uncontrolled Type 2 Diabetic Patients. *Acta Clin Croat*. 2021;60(3):406-

- 414. doi:10.20471/acc.2021.60.03.10
- 80. Cruz GA da, de Toledo S, Sallum EA, et al. Clinical and Laboratory Evaluations of Non-Surgical Periodontal Treatment in Subjects With Diabetes Mellitus. *J Periodontol.* 2008;79(7):1150-1157. doi:10.1902/jop.2008.070503
- 81. Da Cruz Galhardo Camargo GA, De Andrade Lima M, Vieira Fortes T, Salgado De Souza C, Maria De Jesus A, Pacheco De Almeida R. Effect of periodontal therapy on metabolic control and levels of IL-6 in the gingival crevicular fluid in type 2 diabetes mellitus. *Indian J Dent Res.* 2013;24(1):110-116. https://www.ijdr.in/article.asp?issn=0970-9290;year=2013;volume=24;issue=1;spage=110;epage=116;aulast=Galhardo
- 82. GD Gomathi, S Gopalakrishnan, U Sudhakar, A Raghavan, KV Narayan. Effects of Non-surgical Periodontal Therapy on Saliva and Gingival Crevicular Fluid Levels of Chemerin in Periodontitis Subjects With and Without Type 2 Diabetes Mellitus. *Cureus*. 2023;15(1):e33388.
- 83. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ Open. 2016 Aug 12;6(8):e011890.
- 84. Suvan J, Leira Y, Moreno Sancho FM, Graziani F, Derks J, Tomasi C. Subgingival instrumentation for treatment of periodontitis. A systematic review. *J Clin Periodontol*. 2020;47(S22):155-175. doi:10.1111/jcpe.13245
- 85. Tuso P. Prediabetes and lifestyle modification: time to prevent a preventable disease. Perm J. 2014;18(3):88-93.
- 86. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Centers for Disease Control and Prevention (CDC). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. September 26, 2022. Accessed June 15, 2023. https://www.cdc.gov/nchs/nhanes/index.htm
- 87. Taylor JJ, Preshaw PM, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. *J Clin Periodontol*. 2013;40(SUPPL. 14):S113-34. doi:10.1111/jcpe.12059
- 88. Evidence review D for periodontal treatment to improve diabetic control in adults with type 1 or type 2 diabetes: Periodontal treatment to improve diabetic control in adults with type 1 or type 2 diabetes: Evidence review D. London: National Institute for Health and Care Excellence (NICE). Published online June 2022.
- 89. Novaes AB Jr., Gonzalez Gutierrez F, Grisi MF, Novaes AB. Periodontal disease progression in type II non-insulindependent diabetes mellitus patients (NIDDM). Part II—Microbiological analysis using the BANA test. *Braz Dent J*. 1997;8:27-33.
- 90. Thorstensson H, Dahlén G, Hugoson A. Some suspected periodontopathogens and serum antibody response in adult long-duration insulin-dependent diabetics. *J Clin Periodontol*. 1995;22:449-458.
- 91. Feitosa AC, de Uzeda M, Novaes AB Jr. Actinobacillus actinomycetemcomitans in Brazilian insulin-dependent individuals with diabetes mellitus. *Braz Dent.* Published online 1992:35–31.
- 92. Zambon JJ, Reynolds H, Fisher JG, Shlossman M, Dunford R, Genco RJ. Microbiological and immunological studies of adult periodontitis in patients with noninsulin-dependent diabetes mellitus. *J Periodontol.* 1988;59(1):23-31.
- 93. Kolte R, Kolte A, Bawankar P, Bajaj V. Effect of Nonsurgical Periodontal Therapy on Metabolic Control and Systemic Inflammatory Markers in Patients of Type 2 Diabetes Mellitus with Stage III Periodontitis. *Contemp Clin Dent.* 2023;14(1):45-51. doi:10.4103/ccd.ccd 514 21
- 94. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: A tale of two common interrelated diseases. *Nat Rev Endocrinol*, 2011;7(12):738-748, doi:10.1038/nrendo.2011.106
- 95. Polson AM, Caton JG. Current status of bleeding in the diagnosis of periodontal diseases. *J Periodontol.* 1985;56(11):1-3.
- 96. Greenstein G, Caton J, Poison A M. Histologie Characteristics Associated With Bleeding After Probing and Visual Signs of Inflammation. *J Periodontol*. 1981;52(8):420–425.
- 97. Eke PI, Wei L, Thornton-Evans GO, et al. Risk Indicators for Periodontitis in US Adults: NHANES 2009 to 2012. *J Periodontol.* 2016;87(10):1174-1185. doi:10.1902/jop.2016.160013
- 98. Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. *Community Dent Oral Epidemiol*. 2002;30(3):182-192. doi:10.1034/j.1600-0528.2002.300304.x
- 99. International Diabetes Federation. What is diabetes. March 27, 2024. Accessed April 20, 2024. https://idf.org/about-diabetes/what-is-diabetes/
- 100. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA, Genco RJ. Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009-2014. *Journal of the American Dental Association*. 2018;149(7):576-588.e6. doi:10.1016/j.adaj.2018.04.023
- 101. Heasman L, Stacey F, Preshaw PM, McCracken GI, Hepburn S, Heasman PA. The effect of smoking on periodontal treatment response: A review of clinical evidence. *J Clin Periodontol.* 2006;33(4):241-253. doi:10.1111/j.1600-051X.2006.00902.x
- 102. Zandbergen D, Slot DE, Niederman R, Van der Weijden FA. The concomitant administration of systemic amoxicillin and metronidazole compared to scaling and root planing alone in treating periodontitis: a systematic review. *BMC Oral Health*. 2016;16(1). doi:10.1186/s12903-015-0123-6
- 103. Santos CMML, Lira R, Fischer RG, Santos APP, Oliveira BH. Systemic antibiotics in periodontal treatment of diabetic patients: A systematic review. *PLoS One*. 2015;10(12):e0145262. doi:10.1371/journal.pone.0145262

"De zin van het leven ben je zelf"

Jules Deelder

CHAPTER SIX

DMF scores in patients with diabetes mellitus

A systematic review and meta-analysis

L.P.M. Weijdijk, G.A. Van der Weijden, D.E. Slot *Journal of Dentistry. 2023 Sep;136:104628.*



ABSTRACT

Objective

The aim of this systematic review (SR) is to comprehensively and critically summarize and synthesize the available scientific evidence from observational studies that use the decayed-missed-filled (DMF) index to determine caries experiences among adult patients with DM as compared to individuals without DM (non-DM).

Methods

Indices that present examinations of decayed-filled-surfaces (DFS), decayed-missed-filled-surfaces (DMFS), and decayed-missed-filled-teeth (DMFT) established from observational studies were considered. MEDLINE-PubMed and Cochrane Central databases were searched through 1 February 2023 to identify studies that evaluate DMF indices for adult patients with DM compared to non-DM. The reference lists of the selected studies were reviewed to identify additional potentially relevant studies. All studies were independently screened by two reviewers. Included papers were critically appraised using pre-designed forms, and the risk of bias was assessed. Data as means and standard deviations were extracted. A descriptive data presentation was used for all studies. If quantitative methods were feasible, then a meta-analysis was performed. It was decided 'a priori' to perform a sub-analysis on type of DM (I or II). The quality of the studies was assessed.

Results

Initially 932 studies were found, and screening resulted in 13 eligible observational studies. The total number of subjects included in this SR is 21,220. A descriptive analysis of the comparisons demonstrated that eight studies provided data and demonstrated higher DFS (1/2), DMFS (2/3) and DMFT (5/8). This was confirmed by the meta-analysis difference of means (DiffM), which was 3.01 ([95%CI:1.47,4.54], p=0.0001) for DMFT and 10.30 ([95% CI:8.50,12.11], p<0.00001) for DMFS. Subgroup analysis showed that this difference is irrespective to the type of DM (DiffM=3.09;[95%CI:2.09,4.09], p<0.00001).

Conclusion

There is moderate certainty for a higher DMF index score in DM patients as compared to those without DM disease.

INTRODUCTION

Dental caries is one of mankind's most common diseases. The Global Burden of Disease 2010 Study estimates a global prevalence of 35% untreated caries in permanent teeth. This multifactorial condition evolves through a complex interaction over time between acid-producing bacteria, fermentable carbohydrates, and many host factors including teeth and saliva. Tooth decay can lead to loss of teeth, and in a final stage, to tooth lessness also known as edentulism, which is a globally important public health issue because of its high prevalence (exceeding 10% in adults aged \geq 50 years) and associated disability. Periodontal disease, which is an inflammation of periodontal tissues, can also lead to tooth loss if not treated adequately. Both chronic periodontal disease and severe dental caries are the primary reasons for tooth loss in adults.

In diabetes mellitus (DM) the caries process is presumably enhanced.^{2,6} DM is a metabolic disease involving inappropriately elevated blood glucose levels. It is expected that 592 billion individuals in 2035 will have been diagnosed with DM.⁷ The main subtypes of DM are type I and type II, which classically result from defects in the insulin release (type I) or an acquired resistance to insulin in the body (type II). The association between periodontitis and DM has been highlighted in the literature.^{8,9} The relationship between DM and dental caries is complex and sometimes seen as controversial;^{6,10} nevertheless, the prevalence of dental caries is higher and more severe in diabetic patients.^{11,12} The suggested etiology is a decreased salivary flow rate13 and expanded levels of glucose in the saliva.¹⁴ Conversely, in type I DM patients, fewer caries lesions have been reported, which is probably related to the prescribed diet with restricted sugar intake.¹⁵

The most frequently used instrument for recording caries in epidemiological studies, which is recommended by the World Health Organization (WHO), is the decayed-missed-filled (DMF) index. ¹⁶ The index determines the number of decayed (D), missing (M), and filled (F) teeth (T) or dental surfaces (S). ¹⁷ It has been suggested that higher DMF index scores are seen among DM patients, ¹⁸ but the absence of an increased level of caries has also been observed. ¹⁹

Two systematic reviews (SRs) and a meta-analysis were recently performed to evaluate the prevalence of dental caries. Both studies present conclusions of a higher dental caries risk among children and adolescents with type 1 DM.^{12,20} However, no SR with a specific focus on adults and DMF index scores has yet been performed. Therefore, the aim of this SR is to comprehensively and critically summarize and synthesize the available scientific evidence from observational studies that use the DMF index to determine caries experiences among adult DM patients compared to individuals without DM (non-DM).

METHODS

The preparation and presentation of this SR is in accordance with the Cochrane Handbook for Systematic Reviews,²¹ the PRISMA items for reporting in systematic reviews and meta-analyses²² as well the PRISMA for abstracts²³ (Online Appendix S7) and the guideline for meta-analysis and systematic reviews of observational studies in epidemiology (MOOSE).²⁴ An a priori protocol was developed following the initial discussion between the members of the research team. This study is registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD42021232426. The institutional review board of the Academic Centre of Dentistry in Amsterdam also provided approval with the following number: 2021-52834.

Focused question

A precise review question was formulated utilizing the population, exposure, comparison, outcomes, and study (PECOS)²⁵ framework as follows:

What is the effect of DM (exposure) compared to non-DM (comparison) on the DMF (outcome) score, as established from observational studies (study) in adult patients (population)?

This question is based on the hypothesis that the connection between DM and oral health presupposes that the DMF score is higher in DM patients.

Search strategy

A structured search strategy was designed to retrieve all relevant studies that evaluate the DMF, decayed-missed-filled teeth (DMFT), and decayed-missed-filled surfaces (DMFS) scores among patients with DM as compared to non-DM individuals. The search was designed by two reviewers (LPMW and DES). The National Library of Medicine in Washington, D.C. (MEDLINE-PubMed), and Cochrane Central were searched from the inception of the databases through 1 February 2023 for appropriate papers that answer the focused question. Table 1 provides details regarding the search approach employed. No limitations were applied regarding language or publication date in the search engines' search strategy. The reference lists of the studies included in this review were hand-searched to identify additional potentially relevant studies. Additional grey literature was not examined.

Table 1

Search strategy used for PubMed-MEDLINE. The asterisk (*) was used as a truncation symbol.

{[<exposure>] AND [<outcome>]}

<Exposure>

<(Glucose Metabolism Disorders [Mesh]) OR (Diabetes Mellitus [Mesh] OR (Diabetes Mellitus) OR Diabetes OR diabet* OR (glucose metabolism disorders)>

<Outcome:>

<(Dental Caries [Mesh]) OR (dental caries) OR DMF OR DMFS OR DMFT>

The search strategy was customized according to the database being searched.

Screening and selection

A two-stage electronic data search and selection was performed. Titles and abstracts (when available) of all studies identified through the searches were screened. Studies were categorized as eligible, not eligible, or questionable. This process was performed independently by two reviewers (LPMW and DES) using the web tool Rayyan, which expedites the initial screening of abstracts and titles using a process of semi-automation while incorporating a high level of usability.

Predetermined inclusion criteria for the first screening of titles and abstract were as follows:

- The aim or title of the study mentions:
 - Dental caries.
 - DM or any other synonym, such as metabolic syndrome (MetS), as a single disease (no comorbidities by other systemic diseases).
- The title, aim, or abstract of the study mentions:
 - DMF number or specified the DMFS or DMFT number.
- Participants ≥ 18 years old.
- Abstract not available in the database searched.
 - When only the title of the article was available, it was not possible to screen for the aforementioned criteria. Subsequently, reviewers obtained a full paper to read the abstract or full text to check the suitability.

If the information relevant to the screening criteria was not available in the title or abstract, then the paper was excluded. Details of the selected studies that potentially met the inclusion criteria were assessed further. Full-text papers were retrieved for studies that appeared to meet the first set of screening criteria as well as those for which the title and abstract provided insufficient information to make a clear decision. These were read independently by two of the review authors (LPMW and DES).

A full-text review of all potential articles was completed utilizing the second set of eligibility criteria:

- Full-text paper available in English.
- Observational studies, such as cohort, (nested) case-controlled, or cross-sectional studies.
- Studies conducted with human subjects who:
 - Were \geq 18 years old.
 - Had DM as well as a group of non-DM people.
 - Were in overall satisfactory health (no systemic disorders or comorbidities other than DM).
- DM status
 - Either self-reported or clinically assessed.
 - Type of DM: undefined, type I, or type II. Patients with pre-diabetes, gestational diabetes, or MetS components were excluded.
- Reported outcomes:
 - Clinically determined scores.
 - Based on a full-mouth assessment.
 - DMF, DMFT, or DMFS indices were used to measure dental caries.

Any disagreement between the two reviewers regarding study eligibility was resolved after additional discussion. If disagreement persisted, then a third reviewer (GAW) was consulted, whose judgement was considered to be decisive. The reasons for exclusion after full-text reading were recorded (see Online Appendix S1). Thereafter, the selected full-text papers that fulfilled the eligibility criteria were identified and included in this SR; they were also processed for data extraction and estimation of the risk of bias.

Methodological quality assessment

Two reviewers (LPMW and DES) independently scored the individual methodological qualities of the included studies using a comprehensive combination of the critical appraisal checklist for analytical cross-sectional studies, which was developed by the Joanna Briggs Institute, ²⁷ the Newcastle Ottawa scale adapted for cross-sectional studies, ²⁸ and the Risk Of Bias In Nonrandomized Studies - of Exposure (ROBINS-E) tool, ²⁹ as reported by Van der Weijden et al. ³⁰

Judgement of risk of bias is presented according to the seven domains as suggested by the ROBINS-E tool, which consists of:

- Pre-assessment domains: bias due to confounding, bias in the selection of study participants, and bias in the classification of exposure.
- Post-assessment domains: bias due to deviations from the intended exposure, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results.

The judgements within each domain were carried forward to an overall risk of bias. A study was classified as having a *low risk* of bias when all domains were judged to have little bias risk. *Moderate risk* of bias was assigned when one or more domains of the study was judged not to have a higher-than-moderate risk. A study was classified as having *serious risk* of bias when one or more domains was scored as having *serious risk* of bias. An overall critical risk of bias was scored when at least one domain was judged to be at critical risk of bias. The response option *no information* was assigned if the study was judged to be at serious or critical risk of bias and there was a lack of information in one or more key domains.^{27–30} If there was a disagreement between the two reviewers, then a consensus was achieved through discussion. If disagreement persisted, then a third reviewer (GAW) was consulted; this judgement was decisive.

Data extraction

Independent data extraction was performed by two reviewers (LPMW and EEJM) utilizing a specially designed standardized data extraction form. Disagreement between the reviewers was resolved through discussion and consensus. If disagreement persisted, then a third reviewer (DES) was consulted; this judgement was decisive. Data extraction of all included studies having either an observational, cohort, or (nested) case-controlled design were approached as cross-sectional studies. From the eligible papers, details on study design, demographics, number of teeth evaluated, details of DM status, and DMF scores were extracted.

The DMF indices was determined as follows:31

- The DMFT scores concerning decayed, missed, and filled teeth.
 - Total number of evaluated teeth per included study.
- The DMFS scores concerning decayed, missed, and filled surfaces.
 - Total number of evaluated surfaces per included study, with molars and premolars having five surfaces and incisors and canines having four surfaces.
- The DFS scores concerning decayed and filled surfaces.
 - Total number of evaluated surfaces per included study, with molars and premolars having five surfaces and incisors and canines having four surfaces.

When an included study provided multiple age groups, only individuals \geq 18 years of age were considered, and data of those \geq 18 years of age were merged so that these were considered to be one group. When DM patients were presented separately in the original included papers, these groups were merged for the overall analysis. If a DM group was specified in the categories of impaired glucose tolerance or pre-diabetes and DM, then only the diabetics were considered. When possible, a subgroup analysis on DM type, DM duration, or DM status was performed if the original group data allowed for separation of these groups. If a paper provided multiple data based on follow-up examinations, then only the first cohort was considered. When the DMFS index distinguished other surfaces, such as occlusal or buccal, data were merged. For those papers that provided insufficient data to be included in the meta-analysis, the first or corresponding authors were contacted by email to query whether additional data could be provided.

Data analysis

Assessment of clinical and methodological heterogeneity

The factors utilized to assess the clinical heterogeneity of the various studies' outcomes are as follows: characteristics of participants (age, sex, and continent), DM type (I or II), level of DM (controlled, uncontrolled, or both), duration of DM diagnosis, and method of assessment (professionally diagnosed or self-reported DM). Factors employed to assess the methodological heterogeneity were study design details, subject characteristics, and method of DM assessment. Number or number of surfaces of teeth analyzed was either 28 or 32, depending on whether the evaluation included wisdom teeth. The number of reference teeth is 32, according to the WHO.¹⁶ When clinical or methodological heterogeneity was presented across studies, sources of heterogeneity were investigated with subgroup or sensitivity analyses.²¹ Factors that were potentially relevant for subgroup analysis were study design (studies originally designed as cross-sectional evaluations) and participant demographics. For DM-related details, a sub-analysis was planned to examine different types of DM (type I, type II, or type I and II) and total number of evaluable teeth (28 or 32) to explore possible differences.

Descriptive methods

As a summary, a descriptive data presentation was utilized for all studies.

Quantitative methods

The DMF scores among DM patients and non-DM individuals were extracted for each study. Thereafter, the difference of means (DiffM) was calculated between the two groups. Analysis was performed utilizing Review Manager version 5.3.³² An meta-analysis was performed if two or more studies could be included. For both the DMFT and DMFS scores, an meta-analysis was performed to calculate the DiffM as well as its associated 95% confidence interval (CI) and p-value. P-values ≤0.05 were considered to be significant. For a subsequent subgroup analysis, a meta-analysis was performed if more than one study could be included.

The authors of this SR expected that there would be considerable heterogeneity among the included studies, as study designs and details presumably differ. Moreover, DM is not likely to be the single cause for caries. Clinically, DM can vary in its features, which is likely and was the case in the DM population of the included studies. This variance was considered by primarily utilizing the random-effects model, with the exception being when less than four studies were eligible for the meta-analysis. Otherwise, the fixed-effects model was utilized, as advised by the Cochrane oral health group.²¹

Sensitivity analyses were undertaken to evaluate the effect of excluding studies based on specific aspects in the domain of clinical or methodological heterogeneity. Testing for publication bias per outcome was conducted, as proposed by Egger et al.³³ If the meta-analysis involved a sufficient number of trials to make a visual inspection of the funnel plot meaningful (a minimum of 10 trials), then these plots were employed as tools to assess publication bias. The presence of asymmetry in the inverted funnel is suggestive of publication bias.²¹⁻²⁴ As planned, a priori, relative to the type of DM and either 28 or 32 teeth, a subgroup analysis was conducted.

Assessment of statistical heterogeneity

Statistically, heterogeneity was tested by the chi-square test and I^2 statistic. A chi-square test resulting in p<0.1 was considered an indication of significant statistical heterogeneity. As a rough guide to assess the possible magnitude of inconsistency across studies, an I^2 statistic of 0%–40% was interpreted to indicate unimportant levels of heterogeneity. An I^2 statistic of 30%–60% may represent moderate heterogeneity, and an I^2 statistic of 50%–90% may represent substantial heterogeneity. An I^2 statistic of greater than 75% was interpreted to indicate considerable heterogeneity and was further assessed with subgroup or sensitivity analysis. 34,35

Grading the body of evidence

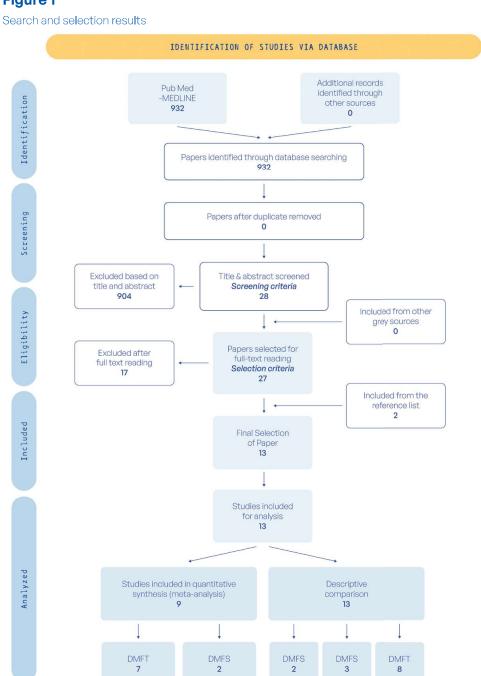
Two reviewers (LPMW and DES) rated the quality of the evidence and the strength of the recommendations according to the following aspects: study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias by utilizing the grading of recommendations assessment, development, and evaluation (GRADE) framework,³⁶ which provides a systematic approach for considering and reporting each of these factors. An overall rating of confidence in effect estimates was considered critical for the final recommendation.³⁷ To interpret the effect, the WHO severity criteria¹⁶ for oral health surveys were used. To summarize the degree of caries experience on the DMFT level, the following levels of caries experience may be considered: <5.0 is very low, 5.0–8.9 is described as low, 9.0–13.9 is considered moderate, and >13.9 is a high caries experience. The levels were converted for the DMFS index (for details, see Online Appendix S2). Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, then the judgement of a third reviewer (GAW) was decisive.

RESULTS

Search and selection results

Searching the MEDLINE-PubMed and Cochrane databases resulted in 932 unique papers, as illustrated in Figure 1. The first screening of the titles and abstracts resulted in 28 papers, for which the full papers were obtained. In the second phase, after full-text reading and contact with the corresponding authors, 17 studies were excluded because they did not meet all eligibility criteria. Other reasons for exclusion are found in the table in Online Appendix S1. Hand-searching of the reference list resulted in two additional papers. Consequently, 13^{10, 13, 19, 38-47} papers were identified and included in this SR. An overview within used study IDs (I-XIII) and their characteristics are presented in Table 2.

Figure 1



Assessment of clinical heterogeneity

Considerable heterogeneity was observed among the 13 included studies. Characteristics of study design, study population, and diagnostic as well as assessment methods are displayed in Table 2. The female sex was more prevalent in four studies, and five studies included more males. In three studies (I, IV, and XII), the sex distribution was unclear. In total, 8,336 women and 11,228 men were included in this SR.

Studies originating from the following continents were present: Europe (III, VI, XIII, and IX), North America (XI and XII), South America (XIII), and Asia (I, II, IV, V, XII, and X) (see Table 2). All studies included a non-DM group in overall satisfactory health who were drawn from the population of the country where the study was performed. The DM participants in five of the included studies (I, IV, V, VI, and VII) were specifically selected from a hospital population.

For inclusion in the individual studies, criteria and diagnoses were clinically assessed for the studies presented herein. The clinical assessments were performed through different methods, such as fasting plasma glucose, glucose, or HbA1c levels. Four papers did not clearly present how the DM status was assessed (I, IV, IX, and X).

In total, five studies specifically focused on type II DM (I, III, IV, X, and XII). One study distinguished between types I and II DM (VIII). For the overall calculation, data from these groups were merged, while the subgroup analysis employed the original group data. Originally, Study XIII also made this distinction; however, the type I DM group included children, so this group was consequently excluded from data extraction and only the data on type II DM patients were utilized. One study reported data on the DM group about poorly and well-controlled individuals (XI). Other characteristics concerning DM patients included short or long duration of DM (IX). Study XII also included a group with a specific focus on impaired glucose tolerance; this group were therefore excluded from data extraction.

 Table 2

 Overview of the included studies and characteristics processed for data extraction

Selection ID	N subjects	Sexes (N	Type of DM	Original conclusion of	Conclusion DMFT/S
Authors	Type of population	males/females)	assessment	the authors	Mean (SD)
Year		Mean age (SD)			Reference teeth
Country		Range in years			
Study design)			
RoB					
I. Jawed et al. (2012)	N: 700 (DM+	DM type II	DMFT scores were	DMFT
		N: 400		found to be	
Pakistan	DM+	¿:&	Type of assessment: ?	significantly high in	DM+
Oross-sectional	Patients of hospital	₫:?	DM for at least 3 years	DM patients than non	14.25 (1.88)
Rob: Moderate		Mean age: 40.94 (9.68)		DM controls.	
	DM-	Range: 26-65			DM-
	General population				10.54 (3.38)
		DM-			
		N: 300			# of Reference teeth: 32 •
		5:€			
		₫: ?			
		Mean age: 41.55 (11.25)			
		Range: 26-65			
II. Seethalakshmi et al.	N:40	DM+	DM type I and II	Mean DMFT was	DMFT
(2016)		N: 20		higher in DM patients	
	DM+	4:14	PD	when compared to	DM+
India	Patients of dental	₫:6	Fasting blood glucose	that of non-DM	8.1 (5.875)
Cross-sectional	school	Mean age: ?	more than 121mg/dl	controls.	
Rob: Serious		Range:?	and a minimum of 2		DM-
	DM-		years disease duration		1.15 (1.461)
	Patients of dental	DM-			
	school	N: 20			# of Reference teeth:?
		\$:16			
		ਹੈ:4			
		Mean age: ?			
		Range:?			

III. Schmolinksy et al. (2019)	N: 3731	DM+	DM type II	Rates in change in	DMFS
		N: 329 (DMFS were	
Germany	DM+	♀ :126 ◊	PD	significantly higher in	DM+
Cross-sectional	General population	ਂ :203 ◊	Self-reported	subjects with poorly-	42.41 ((15.91 ())
Rob: Iow		Mean age: 62.2 ◊	physicians' diagnoses	controlled DM	
	DM-	Range: 20-79	or intake, glucose-	compared to non-DM	Well-controlled
	General population		lowering drugs, HbA1c	subjects.	43.5 🕈 (14.9 💠)
		Well-controlled	levels (≥6.5%), non-		
		N:185	fasting serum glucose		Poorly controlled
		♀ :72 ◊	levels (>11.1mmol/I).		41.0 \(\phi \) (17.2 \(\phi \)
		ु :॥३ ◊			
		Mean age: 63.9 (10.7)			DM-
		Range:?			32.0 • (16.9 •)
		Poorly controlled			# of Reference teeth: 28 •
		N:144			
		♀ :54 ◊			
		ರೆ: 90 ◊			
		Mean age: 60.4 (11.0)			
		Range:?			
		DM-			
		N: 3402			
		♀ :1783 ◊			
		ರೆ:1619 ◊			
		Mean age: 46.3 (15.1)			
		Range: 20-79			

IV. Jawed et al. (2011)	N: 793 (DM+	DM type II	The DMFT indices	DMFT
		N: 398		were found to be	
India	DM+	♀ :200 ◊	Type of assessment:?	significantly high in	DM+
Cross-sectional	Patients of hospital	ರೆ:198 ◊		DM patients as	12.01 (1.54)
RoB: moderate		Mean age: 40.22 (8.97)	DM for at least 3 years		
	DM-	Range: 30-50		compared to non-DM	DM-
	General population			controls.	9.47 (1.24)
		DM-			
		N: 395			# of Reference teeth: 32 •
		♀ : 201◊			
		ೆ :194 ≬			
		Mean age: 39.87 (10.56)			
		Range: 30-50			
V. Cao et al. (2017)	N: 13998	DM+	DM type I/II	Participants with	DMFT
		N: 3571		MetS had higher	
Ohina	DM+	\$:1039	PD	mean numbers of	DM+
Cross-sectional	Patients from	d : 2532	Waist circumference,	fillings, missing teeth	1.75 (1.15)
Rob: Iow	hospital	Mean age: 53.7 (5.9)	triglycerides, blood	and DMFT compared	
		Range: ?	pressure, fasting	to non-DM controls.	DM-
	DM-)	glucose, HDL-c.		1.69 (1.23)
	Patients from	DM-			
	hospital	N:10427			# of Reference teeth:?
		Q :4653			
		3 :5774			
		Mean age: 52.4 (5.8)			
		Range:?			
VI. Bacic et al. 1989	N: 411 (DM+	DM type I/II	No significant	DMFT
		N: 222		difference in the	
Croatia	DM+	Q :92	PD	prevalence of caries	DM+
Cross-sectional	Patients from	♂ :130	C-peptide finding,	and the mean DMFT	17.7 (6.9)
Rob: moderate	hospital	Mean age: 49.6	duration of disease,	level between DM	
		Range:?	mean blood glucose	patients and non-DM	DM-
	DM-		(MBG), HbA1c level,	controls.	14.9 (6.7)
	General population	DM-	presence of diabetic		
		N:189	complications		# of Reference teeth: 32 •
		9 :74			
		♂ :115			
		Mean age: 43.9			
		Range:?			CHAF

VII. Iwasaki et al. (2019)	N: 937	DM+	DM type I/II	There appears to be a	DMFT
		N: 110		positive association	
Japan	DM+	8: 6	PD	between	DM+
Cross-sectional	Patients from	♂ :102	according to the	caries experience and	16 (?)
Rob: moderate	hospital	Mean age: 56	recommendations of	MetS in Japanese	
		Range: 52-61	the Japanese	adults. This	DM-
	DM-		Committee for the	relationship increased	14 (?)
	Patients from	DM-	Diagnostic Criteria of	with the increase in	
	hospital	N: 827	Metabolic Syndrome:	DMFT	# of Reference teeth: 28 •
		Q :321	(presence of central	regardless of dietary	
		d :506	obesity along with >2	habits.	
		Mean age: 52	risk factors: lipid		
		Range: 45-59	abnormality, high blood		
)	pressure,		
			hyperglycemia)		
VIII. Ciglar et al. (2002)	N:153 ◊	DM+	DM type I + II	DM have a	DMFS
		N: 84 ◊		significantly higher	
Oroatia	DM+	¿: ŏ	PD	DMFS-index than	DM+
Cross-sectional	General population	₫: Ş	HbA1c values	the non-DM controls.	22.53 (?)
Rob: serious		Mean age: ≬			
	DM-	Range: 20-45 ♦			Type I
	General population				22.5 🔷 (?)
		Type I			
		N: 60			Type II
		Mean age: 28.7			22.6 🕈 (?)
		:			
		Type II			-MG
		N: 24			21.85 🕈 (?)
		Mean age: 32.6			
		į			# of Reference teeth: ?
		DM-			
		N: 69			
		5:€			
		₫:?			
		Mean age: 30.3			
		Range: 20-45			

IX. Falk et al. (1988)	N: 231 (DM+	DM type I/II	DM and non-DM	DFS
		N:154 ◊		exhibited a similar	
Oross-sectional	DM+	♦ :76 ♦	Type of assessment: ?	caries frequency but	DM+
Sweden	General population	ರೆ:78 ◊		among the diabetics	? (?)
RoB: moderate		Mean age: ?		there was a group of	
	DM-	Range: 20-70 ♦		individuals who had	DM-
	General population	1		more periapical	5 (?)
		Long duration		lesions than the non-	
		N: 82		diabetics.	# of Reference teeth: 28
		mean duration years:			
		28.9		There was no	
				significant difference	
		Short duration		between long and	
		N:72		short duration and	
		mean duration years:		non-diabetics in the	
		5.2		number if teeth and	
				the total number of	
		Long duration		decayed and filled	
		♂:40		tooth surfaces (DFS	
		Q :42		%).	
		Short duration			
		d :38			
		Q :34			
		DM-			
		N: 77			
		Q :43			
		ð :34			
		Mean age: ?			
		Range:?			

X. Latti et al. (2018)	V: 60 \$	DM+	DM type	There was a highly	DMFT
	>	N:30		significant difference	
India	DM+	4:11	Type of assessment: ?	between mean index	DM+
Case-control	Patients of dental	0.19		scores of DMFT in DM	10.67 (5.2)
Rob: serious	school	Mean age: 57.2 ◊		patients and non-DM	
		Range: 30-70		controls.	DM-
	DM-				5.6 (2.59)
	Patients of dental	DM-			
	school	N:30			# of Reference teeth: 32 •
		↓ : □			
		₫:19			
		Mean age: 47.7 ◊			
		Kange, 30-70		i	(1
XI. Lin et al. (1999)	N: 42	- DM+	DM type I/II	The mean	DFS
		N: 24	Well/poorly controlled	decayed/filled surface	
North-America	DM+	4 :14	MO	(DFS) and filled	DM+
Cross-sectional	General (older)	₫:10		surface (FS) scores	57.2 (33.8)
RoB: moderate	population	Mean age: 71	PD	were higher, and the	
		Range: 54-85	Overnight fasting	mean decayed	Well-controlled
	DM-	Well-controlled	plasma glucose test	surface (DS) and	63.4 (26.4)
	General (older)	6:Z	>140 mg/dL confirming	missing surface (MS)	
	population	5 :6	DM, HbA1c for glycemic	scores were lower in	Poorly-controlled
		d :3	control (value 9%) in	non-DM than in DM,	53.3 (38.9)
		Mean age: 73	DM-group, OGTT	and in well controlled	
		Range: 62-85	(control)test in non-DM	MO	DM-
			group (<140 mg/dL)	compared with poorly	79.7 (30.9)
		Poorly controlled		controlled DM.	
		N:15			# of Reference teeth: 32 ◆
		∞: O +			
		0;7			
		Mean age: 70			
		Range: 54-80			
		DM-			
		%I:3			
		⊗.; ◊			
		d :10			
		Mean age: 73			
		Range: 57-86			

XII. Cherry-Peppers et al.	N: 54 ◊	DM+	DM type II	No significant	DMFS
1993		E:Z		difference in DMFS	
	DM+	¿: &	PD	index scores between	DM+
North-America	General population	♂ :?	2-h glucose values	DM and non-DM	53.8 (29.7)
Nested case-control		Mean age: 67.9 (11.1)	according to WHO	controls.	
Rob: moderate	DM-	Range: ?	criteria, HbA1c levels,		DM-
	General population)	OGTT.		56.9 (33.9)
		DM-			
		N: 43			# of Reference teeth: 32
		¿:♦			
		♂ :?			
		Mean age: 60.2 (16.8)			
		Range:?			
XIII. Patiño-Marín et al. 2008	N:70 (DM+	DM type II	No statistical	DMFT
		N: 35		difference in DMFT	
Mexico	DM+	Q :21	PD	index between DM	DM+
Cross-sectional	General population	ರೆ:14 ◊	Blood glucose values,	and non-DM controls.	19.6 (3.9)
RoB: moderate		Mean age: 45 (7.6)	HbA1 values.		
	DM-	Range:?			DM-
	General population				18.2 (3.5)
		DM-			
		N: 35			# of Reference teeth: 28
		Q :25			
		ರೆ:10 ◊			
		Mean age: 42 (9.0)			
		Range:?			

Abbreviations: Rob, risk of bias; N, sample size; & -male; \(\textit{2}\) - female; \(\textit{2}\) is not reported/unknown; \(\textit{3}\), Calculated by reviewers, \(\bullet\) data provided by author, type I and/or II, distinction is made between type of diabetes; PD, professionally diagnoses; OGTT, oral glucose tolerance test; DM+ diabetics, DM-non-diabetics; DMFT, decayed missed filled; \(\textit{8}\) = number

Assessment of methodological heterogeneity

Twelve of the included observational studies utilized a cross-sectional design. One study reported data in a retrospective case-control design (X). Data from Study XI were based on a pilot study. One included paper (III) utilized data from a national study: Study of Health in Pomerania (SHIP), consisting of SHIP-0, SHIP-1, and SHIP-2. Data collection was conducted in SHIP-0 between 1997 and 2001.⁴⁸ SHIP-1 and SHIP-2 comprised follow-up examinations. Therefore, only data from SHIP-0 were analyzed.

The number of evaluated teeth was 32 in six studies (I, IV, VI, X, XI, and XII) and 28 in four studies (III, XII, IX, and XIII). Three studies were unclear regarding which reference number of teeth was used and these could therefore not be used for further meta-analysis.

Study XI originally distinguished between coronal and root surfaces. To establish the overall caries experience, the results of coronal and root surfaces were combined.

Methodological quality assessment

The included case-control studies were classified using a comprehensive combination of the critical appraisal checklist for analytical cross-sectional studies,²⁷ the Newcastle Ottawa scale,²⁸ and the ROBINS-E tool.²⁹ A summary of the methodological quality and potential risk of bias scores is presented in Online Appendix S5. Based on a summary of the bias assessment domains, the estimated potential risk of bias was low for one study (III), moderate for most of the studies (I, IV, V, VI, IX, XI, XII, and XIII), and serious for the remaining studies (II, VIII, VIII, and X).

Description of findings

Table 3 describes and summarizes the statistical differences as reported in the original studies between DM patients and non-DM individuals regarding DMFT/S index values.

Table 3A descriptive summary of statistical significance levels of the difference between DM patients compared to non-DM with regard to DMF, DMFS or DMFT index scores as found in the original papers.

	Study	Exposure	DFS	DMFS	DMFT	Comparison
I.	Jawed et al. 2012	DM			+	non-DM
II.	Seethalakshmi et al. 2016	DM			+	non-DM
III.	Schmolinksy et al. 2019	DM		+		non-DM
IV.	Jawed et al. 2011	DM			+	non-DM
V.	Cao et al. 2017	DM			0	non-DM
VI.	Bacic et al. 1989	DM			0	non-DM
VII.	lwasaki et al. 2019	DM			+	non-DM
VIII.	Ciglar et al. 2002	DM		+		non-DM
IX.	Falk et al. 1989	DM	0			non-DM
X.	Latti et al. 2018	DM			+	non-DM
XI.	Lin et al. 1999	DM	+			non-DM
XII.	Cherry-Peppers et al. 1993	DM		0		non-DM
XIII.	Patiño-Marin et al. 2008	DM			0	non-DM
	TOTAL		1/2 have significant higher DFS (50%)	2/3 have significant higher DMFS (66%)	5/8 have significant higher DMFT (62.5%)	

0: no significant difference, +: DM patients have significant higher index scores than non-DM, 0: no data available, DM, diabetics; non-DM, non-diabetics; DFT, decayed filled teeth; DMFS, decayed missed filled surfaces; DMFT, decayed missed filled teeth.

A total of 13 comparisons of 13 papers could be included: two comparisons of DFS scores, three comparisons of DMFS scores, and eight of DMFT scores. Eight studies provided data and indicated significantly higher DFS in one out of two papers, DMFS in two out of three papers, and DMFT in five out of eight papers. Five studies did not find a significant difference in DMF scores.

Meta-analysis

Studies VII, VIII, and IX provided no SD and could therefore not be used for further analysis. Since there was one study left in the DFS group (XI), the DMFS and DMFT index parameters were used. Consequently, seven papers (I, II, IV, V, VI, X, and XIII) were identified for the meta-analysis on the DMFT data and two papers (III and XII) were employed for the DMFS index parameter. Figures 2 and 3 illustrate that the overall DiffM was 3.01 [95% CI: 1.47, 4.54], p = 0.0001) for DMFT and 10.30 ([95% CI: 8.50, 12.11], p < 0.00001) for DMFS.

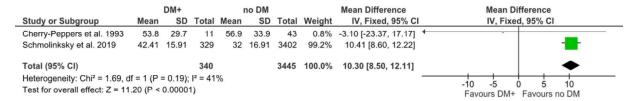
Subgroup analysis for only type II DM exhibited a DiffM=3.09 ([95% CI: 2.09, 4.09], p < 0.00001) and analysis with 32 teeth as a reference point revealed a DiffM=3.29 ([95% CI: 2.37, 4.22], p<0.00001). For details see Online Appendices S3 and S4. An overview of the analysis is shown in Table 4.

Figure 2Forest plot of the meta-analysis on DMFT for DM compared to non-DM, using a random model.

		DM+			no DM			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 Type II									
Jawed et al. 2012	14.25	1.88	400	10.54	3.38	300	16.1%	3.71 [3.29, 4.13]	-
Jawed et al 2011	12.01	1.54	398	9.47	1.24	395	16.2%	2.54 [2.35, 2.73]	
Latti et al. 2018	10.67	5.2	30	5.6	2.59	30	12.5%	5.07 [2.99, 7.15]	
Patino-Marin et al. 2008 Subtotal (95% CI)	19.6	3.9	35 863	18.2	3.5	35 760	13.5% 58.3%	1.40 [-0.34, 3.14] 3.09 [2.09, 4.09]	T-
Heterogeneity: Tau ² = 0.73;	Chi² -	31 22		P - 0 0	0001): 1			5.05 [2.05, 4.05]	
Test for overall effect: $Z = 6$,	,0001), 1	- 30%			
1.1.2 Type I/II									
Bacic et al. 1989	17.7	6.9	222	14.9	6.7	189	14.5%	2.80 [1.48, 4.12]	
Cao et al. 2017	1.75	1.15	3571	1.69	1.23	10427	16.3%	0.06 [0.02, 0.10]	+
Seethalakshmi et al. 2016 Subtotal (95% CI)	8.1	5.895	20 3813	1.15	1.461	20 10636	10.9% 41.7%	6.95 [4.29, 9.61] 3.01 [-0.19, 6.21]	
Heterogeneity: Tau ² = 7.32;	Chi ² =	42.30.	df = 2	P < 0.0	0001): I	$^{2} = 95\%$			
Test for overall effect: $Z = 1$									
Total (95% CI)			4676			11396	100.0%	3.01 [1.47, 4.54]	•
Heterogeneity: Tau ² = 3.76;	Chi ² =	917.50	, df = 6	(P < 0.	.00001);	$I^2 = 999$	6		-10 -5 0 5 10
Test for overall effect: Z = 3 Test for subgroup difference				(P = 0.	96), I ² =	: 0%			Favours DM+ Favours no DM

A chi-square test resulting in a p-value < 0.1 was considered to be an indication of significant statistical heterogeneity. As an approximate guide for assessing the degree of inconsistency across studies, an I2 statistic of 0%-40% was interpreted as might not be important, a statistic of 40%-60%% as possibly representing moderate heterogeneity, 60%-80% as possibly representing substantial heterogeneity and 80%-100% as possibly representing considerable heterogeneity.

Figure 3Forest plot of the meta-analysis on DMFS for DM compared to non-DM, using a fixed model.



A chi-square test resulting in a p-value < 0.1 was considered to be an indication of significant statistical heterogeneity. As an approximate guide for assessing the degree of inconsistency across studies, an I2 statistic of 0%-40% was interpreted as might not be important, a statistic of 40%-60% as possibly representing moderate heterogeneity, 60%-80% as possibly representing substantial heterogeneity and 80%-100% as possibly representing considerable heterogeneity

Table 4

Overview of analysis on DMFT and DMFS for DM compared to non-DM. Presented overall, DM type II and reference teeth.

	Included studies		Effect sizes	sizes		Hetero	Heterogeneity	For details see
		DiffM	Model	95 CI%	p-value	l² value	P-value	
DMFT								
Overall	7 studies	3.01	random	[1.47;4.54]	0.0001	%66	< 0.00001	Figure 2
DM type								
	- VI. Bacic et al. 1989							
=	- V. Cao et al. 2017	1.51	fixed	[0.07;0.11]	0.004	%66	< 0.00001	Online Appendix S3.2
	- II. Seethalakshmi et al. 2016							
	- Jawed et al. 2012							
=	- IV. Jawed et al. 2011	C	0	2.00	5000	ò	0000	
=	- X. Latti et al. 2018	3.07	ralidolli	[2.04,4.04]	-0.0000.	0%0%	0,000,0	Offilitie Appendix 55.1
	- XIII. Patino-Marin et al. 2008							
Reference teeth	teeth							
	- VI. Bacic et al. 1989							
+ 00	- Jawed et al. 2012	C	0	[00 7.4 00]	10000	7000	5000	
	- IV. Jawed et al. 2011	5.27	randonn	[7.5/,4.72]	0.0000	%0%	0.000.0	Offilitie Appendix 64.1
	- X. Latti et al. 2018							
	- V. Cao et al. 2017	900	Ę. C.	[[[0.00]	7000	9070	[0000 0 \	Online Approprise C4.2
	- II. Seethalakshmi et al. 2016	00.0	ם ב	[0.02,011]	0.00	7070	0,000	
DMFS								
- 0	- III. Schmolinsky et al. 2019	00 01	£i,	[11 01:07 0]	10000	70[7	Ċ.	C (2)
	- XII. Cherry-Peppers et al. 1993	10.30	DAXII	[6.50,12.11]	0.0000	0/14	61.0	s ainßi.

A chi-square test resulting in a p-value < 0.1 was considered to be an indication of significant statistical heterogeneity. As an approximate guide for assessing the degree of inconsistency across studies, an I2 statistic of 0%-40% was interpreted as might not be important, a statistic of 40%-60% as possibly representing moderate heterogeneity, 60%-80% as possibly representing substantial heterogeneity and 80%-100% as possibly representing considerable heterogeneity.

Statistical heterogeneity

A minimum of 10 studies was necessary to make a visual inspection of the funnel plot meaningful. However, only seven studies were identified for the meta-analysis and therefore testing for publication bias was not possible. Statistically, heterogeneity was tested and was significant for all performed meta-analysis (presented in Table 4); additionally, all meta-analysis indicated considerable heterogeneity (90%–99%). Sensitivity analyses did not reveal any differences.

Evidence profile

Table 5 presents a summary of the factors employed to establish the body of evidence profile according to the GRADE³⁷ framework relative to the magnitude of the risk based on DMFS/T index scores. The 13 observational studies (portrayed in Figure 1) examined demonstrated that the potential risk of bias was estimated to be low to serious (see Online Appendix S5). Data from the included studies were derived from different populations and continents. Therefore, these findings are considered to be generalizable. Based on the heterogeneity between the included studies, data were judged to be rather inconsistent (presented in Table 4). The data were considered to be rather precise because all selected studies focused on DMFT/S as a primary outcome and because the majority revealed an overlap in the overall 95% CI (illustrated in Figures 2 and 3 as well as in Table 4). As publication bias may have been present, the presence of reporting bias is likely. The 3.01 on DMFT and 10.30 on DMFS index scores is interpreted to mean that it concerns a small effect¹⁶ (see Online Appendix S2). Considering all GRADE aspects, the evidence profile that emerges from this review is that the strength of the evidence is moderate.

Table 5

Summary of findings table of the quality and body of evidence and appraisal of the strength and the estimated evidence profile and of the outcome regarding DMF index scores among DM compared to non-DM.

Determinants of quality	Mean differences			
Study design (Table 2)	Observational studies			
#studies (Figure 1) #comparisons (Table 3)	#13 #13			
Risk of bias (Online Appendix S4)	Low to serious			
Consistency	Rather consistent			
Directness	Rather generalizable			
Precision	Rather precise			
Reporting bias	Likely			
Magnitude of the effect (Figure 2 and 3)	Small			
Strength based on the quality and body of evidence	Moderate			
Summary and direction of the findings	Based on DMF index scores, there is moderate certainty for a higher prevalence of dental caries in DM over non-DM.			

DISCUSSION

Summary of key findings

DM is a common chronic metabolic disease and has been highlighted in the literature with several oral manifestations, such as oral mucosal infections, gingivitis, periodontitis, salivary disfunction and taste impairments.⁴⁹ The present review summarizes the available body of dental and medical literature regarding an important question that examines the association of DM and dental caries in adult populations by using the WHO-recommended DMF index. The results indicate a higher DMF index score for patients with DM as compared to non-DM individuals. This appears to align with reports in other epidemiologic studies.^{12,20}

Selections made

The selection process of the included papers in this SR deviates from the traditional Cochrane approach. However, the foundation is based on similar principles. A two-step approach was utilized to ensure the highest level of accuracy. First, screening of titles and abstracts was performed; second, more specific inclusion criteria were implemented to ensure that the only studies included presented caries activity among DM patients and non-DM individuals. This approach was used previously in an SR concerning the risk of tooth loss in DM patients. 50

Diabetes mellitus and the risk of caries

The risk of caries is caused by many factors, such as caries history, fluoride use, dental plaque, diet, saliva composition and secretion, drug use, and behavioral as well as social factors. ⁵¹ Researchers have proven three risk factors to be causative to caries lesions: cariogenic bacteria, hyposalivation, and frequent ingestion of fermentable carbohydrates. ⁵² Hyperglycemia is associated with decreased salivary secretion, ^{53–55} and reduced saliva secretion as well as lower pH levels due to eating or drinking tends to increase the growth of acidogenic microorganisms. Due to reduced mechanical cleansing, an increased presence of dental plaque and a long-term acidic environment are contributors to caries development. ⁵⁶

Diabetes mellitus comorbidities

DM often appears with other systemic diseases, as they share common risk factors, such as age, sex, smoking, obesity, and socioeconomic status. The sole link between DM and caries is therefore difficult to comprehend. All data included in this SR are based on well-characterized, healthy people and DM patients without other reported comorbidities to avoid bias in the observed association, as other systemic diseases were excluded.

DM is often mentioned as part of people's health status in abstracts of scientific papers. Furthermore, dental caries is regularly mentioned as a component for evaluation of the oral health situation. In the present SR, only papers with a primary focus on DM and DMF index scores were sought and included. These strict inclusion criteria revealed studies that could contribute to answering the research question but had to be excluded. Based on the information in the abstracts, it appears that in these excluded studies, caries experience was greater among DM patients as compared to non-DM individuals. These results corroborate the findings of this SR. It would be of interest to include these studies, however, as these findings are secondary, tertiary, or coincidental, and screening abstracts that are located through a search may lead to an overestimation. However, the inclusion of reported outcomes should not be based on a selection of results that were not the primary focus of the study.⁵⁷ Inclusion of these data may introduce a reporting bias that affects the conclusion drawn.⁵⁸

Diabetic status

There is a positive correlation between glucose concentrations in the saliva and the blood. Scholars have demonstrated that the caries experience is higher among subjects with uncontrolled DM, which could be explained by the excess glucose that enters the oral cavity through saliva and gingival crevicular fluid. Long-term leakage of glucose into the saliva is likely to increase the metabolic activity of the oral microflora. An increased glucose level can favour and increase both aciduric and acidogenic bacteria.

Type I DM can develop at any age but occurs most frequently in children, 63 who were excluded because children can have temporary, mixed, or permanent dentitions which make caries assessments complex for interpretation. As pre-diabetes may be reversible, 64 data from these groups of participants were not considered. Moreover, there remains a discussion about which pre-diabetes cut-off point should be considered and how it can be assessed. 65,66 Additionally, gestational DM was excluded, as it consists of high blood glucose only during pregnancy. 67 It is known that MetS consists of four components: glucose intolerance, abdominal obesity, hypertension, and dyslipidaemia. 68 This combination has been demonstrated to be associated with a higher risk of DM; 69 therefore, to avoid other factors that may be cofactors or risk factors for the present SR, only participants solely diagnosed with DM were considered. Consequently, the relationship of DM with dental caries could be evaluated.

Both types I and II DM are included in this article. Although many risk factors are common to these types of DM, there are some differences, such as dietary habits and medical complications. An SR conducted in 2020 excluded studies that evaluated both types I and 2 patients in one DM group. These authors find that only type I had a significantly higher DMFT compared to controls (-0.55 [95% CI: 1.10, -0.01]), but no difference was found between type II and non-DM individuals (-5.16 [95% CI: 10.62, 0.30]). As the description in the included studies regarding DM is often unclear, the extracted data for this study were merged irrespective of the type of DM. Therefore, it can be difficult to interpret the present findings, as seen in the outcome of the previously published SR. The higher established probability of caries experience in the DM population based on this SR is, however, in the same direction as the mean between both types of the 2020 SR. The higher established probability of caries experience in the population based on this SR is, however, in the same direction as the mean between both

DMF index

DMFT or DMFS indices were used as a measure for dental caries at a tooth or surface level. This is the most frequently used description of caries prevalence in epidemiological studies. The DMFT/S scores provide information about caries prevalence rather than incidence or caries activity. Furthermore, it is not possible to determine when the development of caries begins. Thus, this index cannot provide accurate data about lesions at early stages. This could have resulted in an underestimation of the outcome for this SR. The use of a newer caries classification system, such as the international caries detection and assessment system (ICDAS), could add new information for non-cavitated lesions. When only actual caries cavitation is considered, no differences were found when comparing the ICDAS with the DMFT index. However, in that case, the non-cavitated lesions were not considered. For children a relevant amount of information in estimating disease burden is lost when the DMFT index is used due to incipient or less severe lesions, which are more frequent in this young age group. As the present review is based only on an adult population, the outcome is considered direct and generalizable.

Nevertheless, the differences in the average DMFT and DMFS scores could also be related to the publication dates of the included studies. DMFT scores have been lower in recent studies. This could be explained by the increased attention on oral health and better self-care in recent years^{74,75} as well as the prevalence of caries, which has decreased in developed countries.⁷⁶

Although DMF indices can provide powerful data, the overall score could also include teeth and surfaces that have been lost for reasons other than caries. Especially in DM patients, for instance, periodontitis is also a reason for the loss of teeth. ⁵⁰ Based on the WHO severity criteria, ¹⁶ an index of < 5.0 for DMFT is described as very low. For the present study, DMFT scores were converted to the DMFS index (see Online Appendix S2) and were also classified as very low. Therefore, the magnitude of the effect is small for either DMFT or DMFS.

Evaluable number of teeth

Information on the number of evaluable teeth for the DMFT index score was not available for retrieval in two publications. Therefore, in the meta-analysis, these studies contribute to the overall mean difference only but do not contribute to the sub-analysis on either 28 or 32 teeth (see Online Appendix S4).

Cofactors

The prevalence of DM and the prevalence of caries may differ per region. A decreased prevalence for developed countries is reported. A recent SR⁷⁷ presents the prevalence of DM among subjects with periodontitis by continent, indicating that the highest prevalence of DM was observed in studies from Asian countries (17.2%) and the lowest for those from Europe (4.3%). The overall prevalence of DM in the included cross-sectional studies in this SR is 25.4%, which may indicate a selection bias toward DM or overestimation of DM patients. It is well known that female subjects are underrepresented in medical research, which could be an explanation for the skewed distribution toward the male sexes. This also applies to the present SR: a difference of 2,892 participants in genus is revealed with 8,336 women and 11,228 men. Sex disparities in dental caries have been observed. Other than hormonal variations, it is assumed that there is a lack of evidence regarding sex difference and dental caries. Almost none of the included studies presented the data stratified on sex distribution; therefore, this was not evaluated.

Smoking negatively affects the quality of saliva, as it loses its protective role and becomes an agent in carcinogenesis. ⁸⁰ Only one included paper ⁴² specifically focused on patients who did not smoke. That sample concerns only 40 people out of a total population of 21,220 in this SR, so it is not likely that it contributes to the results. Further studies concerning this aspect are of interest.

Strengths, limitations, and directions for future research

This study is the first SR which determines the relationship between DM and DMF scores as a measure for caries experience with a specific focus on adults.

- Some studies may not be directly comparable since some had very low and other very high caries risk populations.
- The language restriction to English resulted in six potential studies that were excluded (see Online Appendix S1).
- Grey literature was not searched. It is possible that all published studies were not identified.

Despite the limitations, this SR is meaningful and indicates a higher DMF index in DM patients. Further research is needed to establish a better understanding of age, sex, smoking habits, and DM type regarding dental caries in DM patients.

CONCLUSION

There is moderate certainty for a higher DMF index score in DM patients as compared to non-DM individuals.

Online Appendices



STATEMENTS

Acknowledgements

The authors acknowledge Joost Bouwman, head librarian of the Academic Centre for Dentistry Amsterdam, for his help in retrieving the full-text articles. In addition, we thank Z.F. Arrindell for her initial work on this topic and E.E.J. Mayer for her work on extracting data from the included papers.

The authors also are grateful to the following individuals, who authored papers included in this research, for their responses and for the time and effort they contributed to our search for additional data: N. Adachi, B. Holtfreter, D. Božić, Syed M. Shahid, T. Tomofuji, B. Lin, B. Jankovic and B. Latti.

Statement of ethics

An ethics statement is not applicable because this study is based exclusively on published literature. The Institutional review board of the Academic Centre of Dentistry in Amsterdam approved the protocol by number: 2021-52834. This study is registered at the International Prospective Register of Systematic Reviews (PROSPERO) by number CRD42021232426.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Funding sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. For this study, no funding was accepted. The work for this paper was funded by the regular academic appointments of Weijdijk, van der Weijden and Slot at the Academic Centre for Dentistry Amsterdam (ACTA).

Data statement

All data generated or analyzed during this study are included in this article and the onlince appendices. Further enquiries can be directed to the corresponding author.

Author contributions

LPMW: contributed to the design, search and selection, analysis and interpretation, and drafted the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

REFERENCES

The papers included in this synthesis are highlighted in **bold** in the list.

- 1. Marcenes W, Kassebaum NJ, Bernabé E, Flaxman A, Naghavi M, Lopez A, et al. Global burden of oral conditions in 1990-2010: A systematic analysis. J Dent Res. 2013 Jul;92(7):592-7.
- 2. Selwitz RH, Ismail AI, Pitts NB. Dental caries. Lancet. 2007;369(9555), 51-59.
- 3. Nordenram G, Davidson T, Gynther G, et al. Qualitative studies of patients' perceptions of loss of teeth, the edentulous state and prosthetic rehabilitation: a systematic review with meta-synthesis. Acta Odontol Scand. 2013;71(3-4):937-951.
- 4. Peltzer K, Hewlett S, Yawson AE, et al. Prevalence of loss of all teeth (edentulism) and associated factors in older adults in China, Ghana, India, Mexico, Russia and South Africa. Int J Environ Res Public Health. 2014;11(11):11308–11324.
- 5. Wyatt CCL. A 5-year follow-up of older adults residing in long-term care facilities: Utilisation of a comprehensive dental programme. Gerodontology. 2009 Dec;26(4):282–90.
- 6. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. J Am Dent Assoc. 2008;139 Suppl:19S-24S.
- 7. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 2014 Feb 1;103(2):137–149.
- 8. Chapple IL, Genco R; working group 2 of the joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol. 2013;84(4 Suppl):S106-S112.
- 9. Genco RJ, Sanz M. Clinical and public health implications of periodontal and systemic diseases: An overview. Periodontol 2000. 2020;83(1):7-13.
- 10. Latti BR, Kalburge J V., Birajdar SB, Latti RG. Evaluation of relationship between dental caries, diabetes mellitus and oral microbiota in diabetics. J Oral Maxillofac Pathol. 2018;22(2):282.
- 11. Jurysta C, Bulur N, Oguzhan B, Satman I, Yilmaz TM, Malaisse WJ et al. Salivary glucose concentration and excretion in normal and diabetic subjects. J Biomed Biotechnol. 2009:430426.
- 12. Coelho AS, Amaro IF, Caramelo F, Paula A, Marto CM, Ferreira MM, et al. Dental caries, diabetes mellitus, metabolic control and diabetes duration: A systematic review and meta-analysis. Journal of Esthetic and Restorative Dentistry. 2020;32(3):291-309.
- 13. Jawed M, Shahid SM, Qader SA, Azhar A. Dental caries in diabetes mellitus: Role of salivary flow rate and minerals. J Diabetes Complications. 2011;25(3):183–186.
- 14. Mascarenhas P, Fatela B, Barahona I. Effect of diabetes mellitus type 2 on salivary glucose A systematic review and meta-analysis of observational studies. PLoS One. 2014;9(7):e101706.
- 15. lughetti L, Marino R, Bertolani MF, Bernasconi S. Oral health in children and adolescents with IDDM A review. Journal of Pediatric Endocrinology and Metabolism. 1999;12(5 Suppl 2):603-610.
- 16. Petersen PE, Baez RJ, World Health Organization. (2013). Oral health surveys: basic methods, 5th ed. World Health Organization.
- 17. Klein H, Palmer CE, Knutson JW. Studies on Dental Caries: I. Dental Status and Dental Needs of Elementary School Children. Public Heal Reports (1896–1970); 1938. Vol. 53; p.751-65.
- 18. Miralles L, Silvestre FJ, Hernández-Mijares A, Bautista D, Llambes F, Grau D. Dental caries in type 1 diabetics: Influence of systemic factors of the disease upon the development of dental caries. Med Oral Patol Oral Cir Bucal. 2006;11(3):162–6.
- 19. Bačić M, Ciglar I, Granić M, Plančak D, Šutalo J. Dental status in a group of adult diabetic patients. Community Dent Oral Epidemiol. 1989;17(6):313-316.
- 20. Wang Y, Xing L, Yu H, Zhao L. Prevalence of dental caries in children and adolescents with type 1 diabetes: A systematic review and meta-analysis. BMC Oral Health. 2019;19(1):213.
- 21. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.3* (updated February 2022). Cochrane, 2022. Available from: www. training.cochrane.org/handbook, Accessed January 9, 2021.
- 22. Moher D, Liberati A, Tetzlaff J, Altman DG, Antes G, Atkins D, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Int J Surg. 2010;8(5):336-341.
- 23. Beller EM, Glasziou PP, Altman DG, Hopewell S, Bastian H, Chalmers I et al. PRISMA for abstracts: reporting systematic reviews in journal and conference abstracts. PLoS medicine. 2013;10(4): e1001419
- 24. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. J Am Med Assoc. 2000;283(15):2008-2012.
- 25. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environment International. 2018;121(1):1027-1031.
- 26. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst

- Rev 5. 2016;210.
- 27. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R MP, Lisy K MP-F. Critical Appraisal Checklist for Analytical Cross Sectional Studies. Chapter 7: Aromataris E, Munn Z, (editors). The Joanna Briggs Institute; 2017. Available from: https://reviewersmanual.joannabriggs.org/, Accessed 17 June, 2021.
- 28. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2012.
- 29. ROBINS-E Development Group, Risk Of Bias In Non-randomized Studies of Exposure (ROBINS-E). Launch version, 1 June 2022. Available from: https://www.riskofbias.info/welcome/robins-e-tool, Accessed 17 June, 2021.
- 30. Van der Weijden FN, Kuitert RB, Berkhout FRU, van der Weijden GA. Influence of tooth position on wind instrumentalists' performance and embouchure comfort: A systematic review. J Orofac Orthop. 2018;79(3):205-218.
- 31. Petersen PE, Baez RJ, World Health Organization. (2013) . Oral health surveys: basic methods, 5th ed. World Health Organization.
- 32. The Nordic Cochrane Centre. Review Manager (RevMan). Cochrane Collab. 2014.
- 33. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J.1997;315(7109):629-634.
- 34. Van Swaaij BWM, van der Weijden GA, Bakker EWP, Graziani F, Slot DE. Does chlorhexidine mouthwash, with an anti-discoloration system, reduce tooth surface discoloration without losing its efficacy? A systematic review and meta-analysis. International Journal of Dental Hygiene. 2020;18(1):27-43.
- 35. Ryan R; Cochrane Consumers and Communication Review Group. 'Heterogeneity and subgroup analyses in Cochrane Consumers and Communication Group reviews: planning the analysis at protocol stage. Cochrane Consum Commun Rev Group. 2016 Available from http://cccrg.cochrane.org, Accessed June 19, 2021.
- 36. Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: Development and pilot validation. Syst Rev. 2014;3:82.
- 37. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Olin Epidemiol. 2013;66(2):151-157.
- 38. Lin BP, Taylor GW, Allen DJ, Ship JA. Dental caries in older adults with diabetes mellitus. Spec Care Dentist. 1999;19(1):8-14.
- 39. Cherry-Peppers G, Ship JA. Oral health in patients with type II diabetes and impaired glucose tolerance. Diabetes Care. 1993;16(4):638–41.[selection ID: XII]
- 40. Patiño Marín N, Loyola Rodríguez JP, Medina Solis CE, Pontigo Loyola AP, Reyes Macías JF, Ortega Rosado JC, et al. Caries, periodontal disease and tooth loss in patients with diabetes mellitus types 1 and 2. Acta Odontol Latinoam. 2008;21(2):127–33.
- 41. Jawed M, Khan RN, Shahid SM, Azhar A. Protective effects of salivary factors in dental caries in diabetic patients of Pakistan. Exp Diabetes Res. 2012;2012;947304.
- 42. Seethalakshmi C, Jagat Reddy RC, Asifa N, Prabhu S. Correlation of salivary pH, incidence of dental caries and periodontal status in diabetes mellitus patients: A cross-sectional study. J Clin Diagnostic Res. 2016;10(3):ZC12-4.
- 43. Schmolinsky J, Kocher T, Rathmann W, Völzke H, Pink C, Holtfreter B. Diabetes status affects long-term changes in coronal caries The SHIP Study. Sci Rep. 2019 Oct;9(1):15685.
- 44. Cao X, Wang D, Zhou J, Yuan H, Chen Z. Relationship between dental caries and metabolic syndrome among 13 998 middle-aged urban Chinese. J Diabetes. 2017 Apr;9(4):378–85.
- 45. Iwasaki T, Hirose A, Azuma T, Ohashi T, Watanabe K, Obora A, Deguchi F et al. Associations between caries experience, dietary habits, and metabolic syndrome in Japanese adults. J Oral Sci. 2019;61(2):300-306.
- 46. Ciglar L, Skaljac G, Sutalo J, Keros J, Janković B, Knezević A. Influence of diet on dental caries in diabetics. Coll Antropol. 2002 Jun;26(1):311–7.
- 47. Falk H, Hugoson A, Thorstensson H. Number of teeth, prevalence of caries and periapical lesions in insulin dependent diabetics. Eur J Oral Sci. 1989;97(3):198–206.
- 48. John U, Hensel E, Lüdemann J, Piek M, Sauer S, Adam C, et al. Study of Health in Pomerania (SHIP): A health examination survey in an east German region: Objectives and design. Soz Praventivmed. 2001;46(3):186-194.
- 49. Bajaj S, Gupta A, Prasad S, Singh V. Oral manifestations in type-2 diabetes and related complications. Indian J Endocrinol Metab. 2012;16(5):777-779.
- 50. Weijdijk LPM, Ziukaite L, Van der Weijden GA, Bakker E, Slot DE. The risk of tooth loss in patients with diabetes: a systematic review and meta analysis. Int J Dent Hyg. 2022;20(1):145-166.
- 51. Reich E, Lussi A, Newbrun E. Caries-risk assessment. Int Dent J. 1999;49(1):15-26.
- 52. Featherstone JDB, Domejean-Orliaguet S, Jenson L, Wolff M, Young DA. Caries risk assessment in practice for age 6 through adult. J Calif Dent Assoc. 2007;35(10):703-713.
- 53. Siudikiene J, Machiulskiene V, Nyvad B, Tenovuo J, Nedzelskiene I. Dental caries increments and related factors in children with type 1 diabetes mellitus. Caries Res. 2008;42(5):354–62.
- 54. Marder MZ, Abelson DC, Mandel ID. Salivary Alterations in Diabetes Mellitus. J Periodontol. 1975;46(9):567-569.

- 55. Ben-Aryeh H, Serouya R, Kanter Y, Szargel R, Laufer D. Oral health and salivary composition in diabetic patients. J Diabetes Complications. 1993;7(1):57-62.
- 56. Loesche WJ, Syed SA, Laughon BE, Stoll J. The Bacteriology of Acute Necrotizing Ulcerative Gingivitis. J Periodontol. 1982;53(4):223-230.
- 57. Dwan K, Altman DG, Arnaiz JA, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS One. 2008;3(8):e3081.
- 58. Kirkham JJ, Dwan KM, Altman DG, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. BMJ. 2010;340:c365.
- 59. Belazi MA, Galli-Tsinopoulou A, Drakoulakos D, Fleva A, Papanayiotou PH. Salivary alterations in insulin-dependent diabetes mellitus. Int J Paediatr Dent. 1998;8(1):29-33.
- 60. Goyal D, Kaur H, Jawanda MK, Verma S, Parhar S. Salivary pH and dental caries in diabetes mellitus. Int J Oral Maxillofac Pathol. 2012;3(4):13–7.
- 61. Twetman S, Johansson I, Birkhed D, Nederfors T. Caries incidence in young type 1 diabetes mellitus patients in relation to metabolic control and caries-associated risk factors. Caries Res. 2002;36(1):31-35.
- 62. Hintao J, Teanpaisan R, Chongsuvivatwong V, Dahlen G, Rattarasarn C. Root surface and coronal caries in adults with type 2 diabetes mellitus. Community Dent Oral Epidemiol. 2007;35(4):302–9.
- 63. Forouhi, NG, Wareham NJ. Epidemiology of diabetes. Medicine (Baltimore). 2010;38(11):602-6.
- 64. Tuso P. Prediabetes and lifestyle modification: time to prevent a preventable disease. Perm J. 2014;18(3):88.
- 65. James C, Bullard KM, Rolka DB, Geiss LS, Williams DE CC et al. Implications of alternative definitions of prediabetes for prevalence in U.S. Adults. Diabetes Care. 2016;34:387–91.
- 66. Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG PL. Screening for diabetes and prediabetes with proposed Alc-based diagnostic criteria. Diabetes Care. 2010;33:2184–2189.
- 67. CDC. National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States. 2020. Avalaible from: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf, Accessed 9 December 2022.
- 68. Liese AD, Mayer-Davis EJ, Haffner SM. Development of the multiple metabolic syndrome: an epidemiologic perspective. Epidemiol Rev. 1998;20(2):157–72.
- 69. Meigs JB. The metabolic syndrome. BMJ. 2003;327(7406):61–2.
- 70. Shulman JD, Cappelli DP. Epidemiology of dental caries. In: Prevention in Clinical Oral Health Care. 2008;2-13.
- 71. Larmas M. Has dental caries prevalence some connection with caries index values in adults? Caries Res. 2010;44(1):81-84.
- 72. Coelho MAG. ICDAS and dmft/DMFT. Sensitivity and specificity, the importance of the index used: a systematic review. J Dent Public Heal. 2020;11(2):176–87.
- 73. Melgar RA, Pereira JT, Luz PB, Hugo FN, de Araujo FB. Differential impacts of caries classification in children and adults: A comparison of ICDAS and DMF-T. Braz Dent J. 2016;27(6):761-766.
- 74. Levine R. The scientific basis of oral health education. Community Dent Health. 2004;21(2):131-133.
- 75. Dye BA, Tan S, Smith V, Barker LK, Thornton-Evans G, Eke PI, et al. Trends in oral health status; United States, 1988–1994 and 1999-2004. Vital Heal Stat 11, 2007:248:1–92.
- 76. Radić M, Benjak T, Dečković Vukres V, Rotim Ž, Filipović Zore I. Presentation of DMF Index in Croatia and Europe. Acta Stomatol Croat. 2015;49(4):275-284.
- 77. Ziukaite L, Slot DE, Van der Weijden FA. Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies. Journal of Clinical Periodontology. 2018;45(6):650-662.
- 78. Holdcroft A. Gender bias in research: how does it affect evidence based medicine? J R Soc Med. 2007 Jan; 100(1):2–3.
- 79. Martinez-Mier, E. A., & Zandona AF. The impact of gender on caries prevalence and risk assessment. Dent Clin. 2013;57(2):301-315.
- 80. Petrušić N, Posavec M, Sabol I, Mravak Stipetić M. The Effect of Tobacco Smoking on Salivation. Acta Stomatol Croat. 2015;49(4):309-315.

"Als je denkt dat je het niet kunt, dan moet je juist doorzetten"

Aletta Jacobs

CHAPTER SEVEN

Comparing endodontic treatment prevalence in diabetes mellitus and non-diabetic patients

A retrospective case-control investigation

L.P.M. Weijdijk, D.E. Slot, M. el Kadi, G.A. Van der Weijden *International Dental Journal (submitted)*



ABSTRACT

Objective

Apply a case-control retrospective analysis to assess possible differences in the prevalence of endodontically treated teeth in patients with diabetes (DM) and non-diabetics (non-DM).

Methods

A convenience sample of DM and non-DM adults diagnosed with periodontitis and referred to a clinic specializing in periodontal therapy were matched based on age, gender, and year of intake. To assess the number of endodontically treated teeth, a full-mouth set of radiographs was required. Every root-filled tooth was recorded. Sub-analyses were conducted to assess the distribution of teeth based on tooth type and their location in the upper and lower jaws. Additionally, the number of teeth present was counted. Relationships between endodontically treated teeth and related variables were analyzed.

Results

233 periodontitis patients with DM were found to be eligible for inclusion and accordingly matched to 233 periodontitis patients without DM. Between DM and non-DM, no statistically significant differences were found in the mean percentage of endodontically treated teeth (DM: 6.88%; non-DM: 7.34%; P=0.60), tooth type, or jaw type, nor in the average number of teeth (DM: 25.2; non-DM: 25.3; P=0.68). Based on the multivariate analyses with correction for age, smoking status, and number of teeth, DM was not significantly associated with the number of endodontically treated teeth (OR=1.16; 95%Cl: 0.79 <> 1.70; P=0.46).

Conclusion

In matched patient sample with adult periodontitis, there was no significant association between DM appearance and the number of endodontically treated teeth or tooth loss when compared with non-DM. This suggests that in periodontitis patients DM is not a risk factor influencing the degree of tooth decay necessitating endodontic intervention, nor does it appear to contribute to an increased likelihood of tooth loss.

INTRODUCTION

The World Health Organization (WHO) classifies diabetes mellitus (DM) as a significant noncommunicable disease (NCD), responsible for an estimated 1.6 million deaths annually. DM is a complex chronic condition characterized by defects in insulin secretion or acquired insulin resistance within the human body. Due to aging populations and lifestyle factors, DM represents a growing global public health concern, expected to place increasing demands on healthcare systems in the coming decades. Over the years, substantial scientific evidence has established associations between systemic health and oral health, with DM frequently highlighted as a key systemic disorder influencing oral conditions.

According to the Global Burden of Disease Study, dental caries and periodontal diseases are prominent chronic NCDs that necessitate prevention and treatment. Evidence suggests that individuals with DM have an elevated risk of developing both dental caries and periodontitis, the two primary causes of tooth loss. Research indicates that patients with DM exhibit a modest but significantly higher risk of tooth loss compared to non-diabetics (non-DM) individuals. Furthermore, data from 54,936 root canal treatments demonstrated a significant association between DM and an increased frequency of non-retained root-filled teeth.

The biological process of periapical healing following endodontic treatment is found to be impaired in patients with DM, as shown by recent studies reporting negative impacts on periapical healing outcomes in DM populations compared to non-DM controls. This impairment may be attributed to mechanisms such as altered immune responses, cytokine dysregulation, oxidative stress, and impaired neutrophil function. Additionally, DM is associated with heightened inflammation and tissue degeneration, particularly after dental interventions. Hyperglycemia has been implicated in predisposing individuals to dental pulp inflammation and necrosis, which may subsequently increase the need for root canal treatments. However, there is at present no definitive evidence supporting a causal relationship between periapical inflammation and metabolic control of DM. 21

Endodontic therapy is a well-established intervention¹⁶ to preserve teeth—that would otherwise require extraction due to damage or infection.^{22,23} Apical periodontitis (AP), a pathophysiological inflammatory condition primarily caused by microbial infections,²⁴ often arises in necrotic or previously treated pulp tissue. In some cases, infections extend into peri-radicular tissues, resulting in acute or chronic abscesses.²⁴ Emerging evidence indicates a bidirectional relationship between AP and DM.²⁵ For instance, a Brazilian study identified significant associations between AP and DM or prediabetes in a rural population.²⁶ Conversely, AP has also been linked to an increased risk of DM.²⁷ These findings underscore the need for tailored clinical management of DM patients, who may experience more frequent and chronic AP with a tendency toward non-healing outcomes.²⁸ Notably, a retrospective cohort study revealed that patients with periodontal disease also exhibit a higher risk of developing AP in endodontically treated teeth compared to those without periodontal disease.²⁹

A histological study examining caries-free teeth with varying degrees of periodontitis demonstrated that pathological changes may occur in the pulp when periodontal disease is present.³⁰ However, the pulp remains viable as long as the apical foramen is not compromised, suggesting that periodontal disease rarely jeopardizes the vital functions of the pulp unless it progresses to a terminal stage involving the primary pulpal blood supply.³¹ Clinical studies, however, highlight a reverse association between periodontitis and endodontic pathology. In patients with periodontitis, the marginal bone level has been correlated with both the percentage of root-filled teeth and the percentage of root-filled teeth with AP.³² A significant relationship was observed between periapical pathology and vertical bony defects, with teeth exhibiting periapical pathology showing significantly deeper periodontal pockets compared to those without. In mandibular molars with periapical lesions, significantly greater mean

periodontal probing depths have been reported compared to teeth without such lesions, alongside a higher frequency of horizontal furcation involvement.³³ Teeth with progressing periapical pathology demonstrated greater radiographic attachment loss than those without periapical pathology. Notably, an approximate threefold increase in the rate of marginal proximal radiographic bone loss was observed.34 These findings underscore the potential for AP, evident as periapical radiolucencies, to exacerbate periodontitis progression,³⁵ likely through the spread of endodontic pathogens via patent accessory canals and dentinal tubules. Given the elevated risk of AP in diabetic patients, 29 it is of interest to investigate whether this predisposition translates into a higher prevalence of endodontic treatments. This is particularly relevant as asymptomatic tooth infections are common and may go unnoticed, and untreated.³⁶ Moreover, inadequately managed caries in DM patients—who are reported to be more susceptible to tooth decay³⁷—can progress into deeper lesions, ultimately leading to pulp necrosis.38 A recent systematic review (SR) reported a marginally significant finding of nearly double the prevalence of root canal treatments in DM patients compared to non-DM controls.³⁹ Similarly, a cross-sectional study observed a higher number of endodontically treated teeth in DM individuals compared to non-DM.⁴⁰

The present study aimed to evaluate in a matched patient group with periodontitis the prevalence of endodontically treated teeth, comparing those with DM to those without.

METHODS

Design and ethics

This study was prepared according to the guidelines suggested by the STROBE and RECORD checklists (see Online Appendix S1 and S2). These checklists provide recommendations of items to include in reports of observational studies.^{41–43} Approval by a Review Board for Human Research was not required.⁴⁴ The institutional review board of the Academic Centre for Dentistry Amsterdam (ACTA) approved the protocol under reference number 2021-11526 (see Online Appendix S3).

Data set of the studied population

The patient population was a convenience sample from the Clinic for Periodontology in the city of Utrecht, the Netherlands, which is a private clinic specialized in- and restricted to periodontology. The rationale for selecting this study population was that for periodontitis patients usually a full set of radiographs is available for diagnosis and treatment planning. Also, the prevalence of DM was considered to be higher among periodontitis patients than among a random patient sample. Patient record files were available from the Dental Practice Management Software Package Simplex (Gé Systems, the Netherlands B.V.) and radiographs from the image analysis software VisiQuick (Citodent Imaging B.V., Amsterdam, the Netherlands). The dataset was comprehensively compiled through a retrospective analysis of the medical records encompassing all patients who received treatment between 2003 and 2019. The included patients had given their approval for their medical records to be used for scientific and quality evaluation purposes by signing an informed consent form prior to the intake appointment.

Diagnosis, status, and case selection Periodontal diagnosis

All included patients were diagnosed with moderate to severe adult periodontitis based on the criteria proposed by van der Velden, 47.48 which expresses the extent of periodontal disease by considering the number of affected teeth and the severity of disease based on bone and attachment loss. Only patients with adult periodontitis (\geq 36 years) were considered.

Diabetic status

All patients completed an extensive health questionnaire, which included DM status (answered binary as yes or no), at intake. It was standard procedure for the periodontist to verbally confirm positive responses on the medical history document. As quality indicator, the DM patients were listed, and the prevalence was calculated as previously outlined in an earlier publication. ⁴⁹ For this analysis, the DM cases were defined prior to further data extraction. No distinction was made between type I and II DM. Patients with an unclear DM status were excluded.

Case and control selection

Each DM case was matched to an non-DM control to evaluate the differences between groups. The matching procedure was performed by two researchers (MK and LPMW) in the following order: gender, year of birth, in agreement with Paljević et al. (2024)¹⁴ and Poyato-Borrego et al (2020)⁵⁰ with in addition matching based on the year of intake. Matching was continued until every DM case had a corresponding eligible control match. Age variations of one year were

allowed if matched pairs were not born in the same year or visited the clinic for the first time in different calendar years. When more than one matched non-DM control was available, the individual whose date of birth most closely approximated that of the DM subject was chosen.

DM patients and their matched controls were deemed suitable and selected for inclusion based on the following inclusion criteria:

- Aged 36 years or older.
- Diagnosed with moderate to severe adult periodontitis based on the criteria established by van der Velden.⁴⁸
- Availability of comprehensive clinical records and radiographic data, including full-mouth radiographs, for thorough evaluation.
- Completion of a detailed health questionnaire, including self-reported DM status.
- Signed informed consent permitting the use of medical records for research purposes.

Data extraction

Procedure

Of the selected DM and non-DM cases, patient record files were manually reviewed, and data were extracted individually by two researchers (MK and LPMW). Any disagreement was resolved through discussion and consensus. A third reviewer (GAW) was consulted if required, and his judgment was considered to be decisive. Data extraction was performed by utilizing a custom-designed, standardized data extraction form. Extracted data were entered into a Microsoft Excel file and saved and could only be accessed with a password known to the research team.

The following parameters were extracted from eligible patient records: gender, age, year of periodontal intake, periodontal diagnosis, DM status, number of endodontically treated teeth, number of teeth, percentage of teeth and sites with probing pockets (PPD) >5mm, and smoking behavior. To ensure complete anonymization, any data associated with individual patients was deleted from the final dataset after the extraction was complete. When clinical data for a DM case were incomplete or missing, the case and non-DM match were excluded from analysis. If information was incomplete or missing for an non-DM case, the case was excluded from analysis, and a new match for the DM case was sought. This approach was also applied for incomplete and missing radiographic data.

Radiographs

Patients with a full set of dental radiographs were included. A set was deemed complete if peri-apical radiographs of all teeth were present or if a panoramic radiograph was available. A timeframe of one year was allowed between radiographs and the time of the periodontal intake clinical examination.

Number of teeth and endodontic treatment

The number of teeth and endodontically treated teeth were scored on radiographs and categorized according to type: molars, premolars, or anterior teeth (canines and incisors) and subdivided into upper and lower jaw. Teeth that contained any form of root-canal obturation were assessed as endodontically treated. Additionally, the number of teeth was extracted from records based on the periodontal chart to ensure the correct number of teeth were assessed.

Pocket probing depth

In order to obtain a measure of periodontitis severity records from the periodontal intake appointments were reviewed for periodontal status. For this purpose, data on the number of teeth and total number of sites with PPD of >5 mm⁵¹ were extracted.

Smoking habits

Smoking habits were recorded from the medical questionnaire file and divided into three categories: current smoker, former smoker, and non-smoker. The number of cigarettes smoked per day was also recorded.

Analysis

The anonymized raw data set in Excel (Microsoft Corporation) was transferred to the statistical analysis computer package, IBM SPSS Statistics 27 (Armonk, USA). Means, standard deviation, and frequency were used to generally describe the obtained data.

First, parametric tests were performed. Case and control subjects were directly compared using independent t-tests and $\chi 2$ (Chi-square) tests to assess possible variances between the groups demonstrated by 95% confidence intervals (CI), and P-values by difference between groups. Characteristics such as gender, age, and smoking habits were analyzed. Additionally, analysis was performed for the following variables: number of teeth, percentage of endodontically treated teeth, percentage of teeth with PPD >5 mm, and percentage of sites with PPD >5 mm. Percentages were calculated to correct for the total number of teeth for each individual. It was decided 'a priori' to perform sub-analyses for the number of endodontically treated teeth per tooth type and jaw type.

Second, multivariate logistic regression analyses were performed using a series of independent variables (DM, age, smoking, and number of teeth) to find the best fitting subset of risk indicators that predict the dependent variable: endodontically treated teeth. Odds ratios (OR) with 95% CI were calculated. For significant findings, the OR were interpreted according to Chen et al. $(2010)^{52}$ as equivalent to Cohen's d. Less than 1.68 was interpreted as no effect, \geq 1.68 as small effect, \geq 3.47 as medium effect, and \geq 6.71 as large effect. Overall, the level of significance was set at $P \leq$ 0.05.

Post hoc power analysis

'Post hoc' power analysis was performed using statistical software (G power v.2.0, Bonn, Germany) to confirm based on the sample size the study power. A minimum of 80% power was considered necessary to confirm that the sample size was adequate for detecting statistically significant differences.

RESULTS

Characteristics

In total, 344 DM visited the clinic between 2003 and 2019, of which 111 were not eligible to be included in this study according to the predefined criteria. The most common reason for exclusion was lack of full mouth radiographic information. Another common reason for exclusion was incomplete DM status. The 233 included periodontitis patients with DM were matched with 233 eligible periodontitis patients without diabetes, resulting in 466 cases and controls eligible for statistical analysis. The subjects ranged from 42 to 87 years of age, with a mean age of 65 years. In total, 54.9% of the subjects were male and 45.1% were female in the DM group, while, in the non-DM group, 53.6% were male and 46.4% were female. In the DM group, 57% were smokers or former smokers. This was the case for 60% of the non-DM group. The mean number of cigarettes for those that still smoked was 12.76 per day for the DM and 13.13 for the non-DM. Analysis of the demographics showed no statistically significant difference resulting from proper matching.

Severity of periodontitis

The mean percentage of teeth with a pocket depth >5mm at patient level was 40% for DM and 39% for non-DM (P=0.64). The mean percentage sites with pockets >5mm at patient level was 16% and 15%, respectively. There was no significant difference between the groups in the percentage teeth (P=0.64) or sites (P=0.68).

Number of (endodontically) treated teeth

The mean number of remaining teeth was 25.2 (4.03) for the DM and 25.4 (3.94) for the non-DM controls. Of the 233 diabetes patients, 153 had at least one endodontically treated tooth (66%), compared to 145 in the control group (62%). The mean percentages of endodontically treated teeth were 6.9% (9.23) and 7.3% (9.62) for DM and non-DM respectively. There was no significant difference between the groups regarding the mean number of teeth (P= 0.68) or the percentage of endodontically treated teeth (P=0.60).

Table 1Characteristics of the included periodontitis patients and separated by matched DM status

		Patients		Sta	ntistical analysis
	DM N=233	Non-DM N=233	Total N=466	Difference DM/non-DM	Test
Sex Male (%) Female (%)	128 (54.9%) 105 (45.1%)	125 (53.6%) 108 (46.4%)	253 213	3 -3	0.78*
Age in years Mean (SD) Range	65.12 (10.15) 42 - 86	65.23 (10.06) 42 - 87	65 42 - 87	-0.09	P=0.90 95%Cl:[-1.96<>1.72]**
Smoking status No smoker (%) Current smoker (%) Former smoker (%)	100 (42.9%) 62 (26.6%) 71 (30.5%)	94 (40.3%) 75 (32.2%) 64 (27.5%)	194 137 135	6 (2.6%) -13 (5.9%) 7 (3.0%)	0.41*
Smoking status No smoker/former smoker Current smoker	174 59	158 75	331 135	15 - 15	0.13*
Mean number of cigarettes/day	12.76 (8.39)	13.13 (7.31)		-0.37	P=0.79 95%CI: [-2.32<>3.06]**
Patients with an endodontically treated tooth (%)	153 (66%)	145 (62%)	298	8	0.44*
	Se	verity of periodor	ntitis (patier	nt level)	
Mean % of teeth with pocket depth >5mm	40.08% (24.80)	38.92% (28.88)		1.16%	P=0.64 95% CI: [-6.06<>3.74]
Mean % sites with pocket depth >5mm	15.91% (13.17)	15.39% (14.11)		0.53%	P=0.68 95% CI: [-3.01<>1.96]

 $Abbreviations: DM: diabetes\ mellitus-non-DM: no\ diabetes\ mellitus-N: sample\ size-SD: standard\ deviation-CI: confidence\ interval$

^{*}Chi² test ** Independent T-test

Table 2.1

Number of teeth, endodontically treated teeth, presented as mean and standard deviation of the included DM cases and their matched non-DM controls

	Mear	(SD)		Statistical and	alysis
N=466	DM N=233	Non-DM N=233	Difference	95% CI	Test*
Mean number of teeth	25.20 (4.03)	25.35 (3.92)	0.15	[-0.57<>0.88]	P=0.68
Total number of teeth	5871 (4.03)	5907 (3.94)	36		
Mean number of endodontically treated teeth at patient level	1.65 (2.13)	1.80 (2.31)	0.15	[-0.26<>0.55]	P=0.48
Mean % endodontically treated teeth at patient level	6.88% (9.23)	7.34% (9.62)	0.87%	[-1.25<>2.18]	P=0.60

Abbreviations: DM: diabetes mellitus – non-DM: no diabetes mellitus – N: sample size – SD: standard deviation – OI: confidence interval

Table 2.2

Sub- analysis of jaw and type of endodontically treated teeth on patient level presented as mean and SD of the included DM cases and the matched non-DM controls.

	Mean (SD)		Statistical analysis		
N=466	DM N=233	Non-DM N=233	Difference	95% CI	Test*
Maxilla (SD)	0.98 (1.44)	1.13 (1.56)	0.15	[-0.12<>0.42]	P=0.28
Mandibulae (SD)	0.67 (1.03)	0.67 (1.12)	0.00	[-0.20<>0.19]	P=0.97
Molars (SD)	0.74 (1.10)	0.77 (1.15)	0.03	[-0.18<>0.23]	P=0.81
Premolars (SD)	0.53 (0.94)	0.63 (1.08)	0.10	[-0.09<>0.28]	P=0.29
Anterior (SD)	0.38 (0.89)	0.40 (0.90)	0.02	[-0.14<>0.18]	P=0.80

Abbreviations: DM: diabetes mellitus – non-DM: no diabetes mellitus – N: sample size – SD: standard deviation – CI: confidence interval

Sub-analysis

The sub-analysis of the number of endodontically treated teeth regarding the lower or upper jaw revealed no statistically significant differences between DM and non-DM patients (95%CI:-0.20<>0.19 and P=0.97, and 95%CI:-0.12<>0.42 and P=0.28, respectively). To evaluate possible differences per type of tooth, an additional sub-analysis was performed. This subdivision by molars, premolars, and anterior teeth revealed no statistically significant differences between DM and non-DM patients.

Analysis

The continuous value of endodontically treated teeth was dichotomized and used for the regression model. When only DM was accounted for, the crude OR was 1.16 (95%Cl:0.80<>1.70;P=0.44). Additionally, the analysis examined the association between

^{*}Independent T-test

^{*}Independent T-test

endodontically treated teeth and DM-related factors, including age smoking status and number of teeth (see Online Appendix S4). Table 3 summarizes the OR estimates and associated 95% confidence intervals. The OR does not change in the multiple linear regression analysis with correction for age, smoking and number of teeth. DM was not significantly associated with endodontically treated teeth (OR=1.16;95%Cl:0.79<>1.70;P=0.46). In addition, the effect of current and former smoking status and DM on the extent of endodontically treated teeth was explored using nonsmoking as a reference. The OR increased for current smokers (OR=1.57) and showed a tendency towards statistical significance (P=0.06) compared to people who never smoked. The OR being less than 1.68 this can be interpreted as no effect.⁵² For former smokers, this comparison resulted in an OR of 1.31 (P=0.27).

Post hoc power analysis

The 'post hoc' power analysis estimated that a minimum inclusion of 65 subjects per group would achieve an 80% statistical power for the study.

 Table 3

 Multiple logistic regression on endodontically treated teeth

Independent variables	OR (95% CI)	P-value
DM	1.156 (0.785–1.704)	0.462
Age*	1.038 (1.017-1.059)	<0.001
Total number of teeth	0.973 (0.922-1.027)	0.324
Smoking (3 categories: non- smoker, former smoker, current smoker)	1.167 (0.922–1.478)	0.199

Abbreviations: DM: diabetes mellitus - CI: confidence interval - OR: odds ratio

Table 4Multiple logistic regression on endodontically treated teeth with smoking as categorial variable

Independent variables	OR (95% CI)	P-value
DM	1.175 (0.797-1.734)	0.416
Age*	1.039 (1.018-1.061)	<0.001
Total number of teeth	0.977 (0.925–1.031)	0.396
Smoking Status Non-smoker**		
Current smoker	1.565 (0.976–2.510)	0.063
Former smoker	1.306 (0.817–2.089)	0.265

Abbreviations: DM: diabetes mellitus - CI: confidence interval - OR: odds ratio

^{*}Continuous variable

^{*}Continuous variable, **Reference category

DISCUSSION

DM is one of the most prevalent chronic medical conditions among dental patients.⁵³ Although DM's bidirectional link with periodontal disease has been thoroughly discussed, less is known about its influence as a disease-modifying factor in the progression of caries lesions and incidence of AP. This retrospective analysis aimed to evaluate the difference in the percentage of endodontically treated teeth between DM patients and non-DM controls among a convenience sample of referred periodontitis patients. The prevalence of root-canal-filled teeth was a surrogate for pulpal necrosis that among other reasons may have resulted from extensive tooth decay. The results in our sample showed DM was not a clinically relevant risk factor for the prevalence of endodontically treated teeth or tooth loss.

Justification of convenience sample

The referral population in this retrospective case-control analysis was a convenience sample from a private periodontal clinic, mainly because full sets of patient radiographs are usually available due to diagnostic purposes,⁴⁵ thereby allowing for a large patient sample with adequate radiographic information. All patients had been professionally diagnosed with periodontitis, and matching from the same patient periodontitis population was considered a fitting approach to compare groups with and without DM. Although periodontitis is linked to DM, current evidence does not support a higher incidence of caries in periodontal patients. As reported in the European Federation of Periodontology (EFP),⁵⁴ DM has been established as a risk factor for periodontitis but has not been shown to influence caries prevalence directly. This suggests that a sample of periodontitis patients does not inherently bias results related to caries experience.

The possible role of DM as a risk factor for AP, in part as a surrogate for extensive tooth decay resulting in pulpal necrosis, was assessed by comparing the number of endodontically treated teeth between DM and non-DM. No statistically significant differences were found regarding the percentage of endodontically treated teeth, the number of endodontically treated teeth per jaw or tooth type, or the number of teeth in general. This observation is supported by similar findings from a Brazilian non-periodontal patient sample, showing an average number of teeth in DM of 21.7 and 22.8 in non-DM (P>0.05) and an average of 2.8 and 3.4 for endodontically treated teeth (P>0.05). However, in this Brazilian population AP was significantly more prevalent in untreated teeth from type II DM (15% versus 12% in non-DM controls). Two prospective studies that have compared the outcome of root canal treatment in DM and non-DM supported this supposition. It is therefore presumed that DM cannot be ruled out as a disease modifier of AP.

Diabetes and tooth decay

The literature provides little or no consistent information on the role of DM as an etiological factor for tooth decay. It has been suggested that uncontrolled DM may result in an increased prevalence of dental caries. ⁵⁸ However, a SR found the literature does not describe a consistent relationship between type I DM and dental caries. ⁵⁹ This is supported by a recent scoping review concluding there is limited clinical evidence to support a clear relationship between hyperglycemia and dental caries in humans. ⁶⁰ In contrast, long-term hyperglycemia was found to induce dental caries in type I and type II diabetic rodents. ⁶⁰

Diabetes and pulpal inflammation

A recent SR concluded that DM increased inflammation/degeneration, especially after dental procedures. An increased state of inflammation in the case of hyperglycemia could result in a diminished healing of apical tissues. Furthermore, a more intense state of inflammation can be observed at the peri-apex of diabetics. Higher rates of inflammation may lead to an uncontrolled DM state due to a rise in blood glucose levels. Description of the case of hyperglycemia could result in a diminished healing of apical tissues. The case of hyperglycemia could result in a diminished healing of apical tissues. Description of the case of hyperglycemia could result in a diminished healing of apical tissues. Description of the case of hyperglycemia could result in a diminished healing of apical tissues. Description of the case of hyperglycemia could result in a diminished healing of apical tissues. Description of the case of hyperglycemia could result in a diminished healing of apical tissues. Description of the case of hyperglycemia could result in a diminished healing of apical tissues. Description of the case of hyperglycemia could result in a diminished healing of apical tissues. Description of the case of hyperglycemia could result in the case of hyperglycemia could result in a diminished healing of apical tissues. Description of the case of hyperglycemia could result in the case of hyperglycemia could re

DM has been suggested as a negative factor regarding success of endodontic treatment. A significant association between the presence of periapical radiolucencies in root-filled teeth amongst diabetics has been shown, thereby reaffirming the suggestion that DM may negatively impact endodontic outcome and healing. In Europe, it is estimated that periapical radiolucencies affect 61% of individuals and 14% of teeth, and that prevalence increases with age. In Globally, the prevalence of AP is estimated at 52% at the individual level and 5% at tooth level. This is in line with the present evaluation (See Table 1). A retrospective analysis of a Spanish university sample with 70 subjects showed that the prevalence of periapical radiolucencies was significantly higher in patients with DM type II than in non-DM controls. Another cross-sectional Spanish sample with 100 subjects found that people with DM had a significantly higher chance of at least one root-filled tooth compared to non-DM controls (70% and 50%, respectively).

As the purpose of the present retrospective case control analysis was to assess the percentage of endodontically treated teeth as the outcome parameter, no attempt was made to evaluate presence of periapical radiolucencies nor success of endodontic treatment. Overall analyses and sub-analyses found the prevalence of root filled teeth in DM patients was not higher than in non-DM controls.

Diabetes and tooth loss

Endodontic therapy is generally a predictable treatment, resulting in a retention rate of up to 97% for treated teeth. However, approximately 3% of endodontically treated teeth require further treatment, which is most frequently extraction of the tooth. Endodontically treated teeth are prone to extraction mainly due to non-restorable carious destruction. A recent SR that used the DMF index to determine caries experience found higher scores in DM patients compared to non-DM. In the current study population, the number of remaining teeth between the DM and non-DM controls with periodontitis was not significantly different. Another retrospective analysis showed comparable results, concluding there was no significant difference in the total number of teeth between these two groups. These findings are not in line with a recent SR, which found DM patients had a significantly higher risk of tooth loss. However, the risk ratio was found to be 1.63, which, although significant, was interpreted as a 'small effect'. Moreover, poorly controlled DM is particularly a significant risk factor for tooth loss. As it was not possible to incorporate the DM control status for the present retrospective analysis, no distinction and sub-analysis between well-controlled and poorly controlled DM could be made.

Diabetes and periodontitis

The relationship between periodontal disease and DM is a subject many authors have attempted to define. According to a Cochrane library review, the number of studies conducted on the link between DM and periodontitis has increased significantly in the past decade. In 2013, a consensus report on DM and periodontal disease was published by the European Federation for Periodontology and American Academy for Periodontology. This report reviewed epidemiological evidence from cross-sectional, prospective, and intervention studies on the role of periodontitis in DM and the underlying mechanisms. Periodontitis is proposed

to adversely affect glycemic control in DM. Moreover, a direct relationship was described between the severity of periodontal disease and DM-related complications. Although the findings with respect to periodontal disease severity (See Table 1) were not the primary purpose of this retrospective analysis, the mean percentage of periodontal pockets >5mm was used as an indicator for the extent of periodontitis. In this study, the percentage of pockets >5mm was found to be similar between DM and their matched controls. The present findings when considering pocket depth >5mm as indicator for disease severity therefore do not support the supposition that periodontal conditions are significantly worse in DM periodontitis patients compared to non-DM periodontitis controls.

The present study retrospectively analyzed data from patient records that involved periodontal treatment in the period of 2003–2019. At that time, patients were classified at intake according to the definition of Van der Velden. Based on age, those patients that were classified as "adult periodontitis" were selected for the present evaluation of treatment success. Given the new classification which was more recently introduced patients would now be classified as having periodontitis. Therefore, it is difficult to compare this study direct to other studies that involve periodontal disease after 2018.

Smoking and endodontic treatment

While smoking is considered as a risk factor for periodontitis, studies have shown no difference between smokers and non-smokers in terms of AP.71 In the present analysis the OR (1.57) for current smokers was close to being significant (p=0.06). A cohort study conducted at the University of Basel, which included full-mouth periapical radiographs of 161 subjects (66 current smokers, 28 former smokers, and 67 individuals who had never smoked), found that smoking status did not predict AP in either females or males within this sample group.72 However, another study in a Portuguese population demonstrated that smoking increased the probability of developing AP.73 These contrasting findings highlight the controversial nature of the association between smoking habits and endodontic infection.21 It is also shown that both DM and smoking can impair the non-specific immune system and alter pulp and periapical healing after endodontic treatment.21 In the present analysis, no attempt was made to evaluate the success of the endodontic treatment. Nonetheless, it can be hypothesized that tobacco smoking is a negative prognostic factor for the outcome of root canal treatment, based on the outcome of a SR conducted in 2020.74 However, the overall strength of evidence was found to be low.

Strengths and limitations

As the most important strength of this study, the distribution of age and gender was well-matched for the DM and non-DM controls. Additionally, the population size of over 450 cases and controls contributes to the robustness and statistical power of the study. As part of the data extraction, the percentage of pockets >5mm and smoking status of the included subjects were recorded. No difference between the two studied groups could be found. With this approach, the potential confounding factors were excluded, and the most reliable and valid estimation of the difference in the number of endodontically treated teeth between DM patients and non-DM controls could be analyzed.

On the other hand, this retrospective analysis had several limitations, as it did not differentiate between DM type I and type II. Previous research shows that DM types I and II interact differently regarding general health. Moreover, DM that was poorly controlled was not differentiated from DM that was effectively controlled by a physician and/or patient.

Also, DM prevalence was assessed via self-report based on a medical history form and checked

verbally by the periodontist at the intake appointment. Self-reported data are often argued to be unreliable and threatened by self-reporting bias.⁷⁵⁻⁷⁷ Moreover, it is possible the controls were not aware or did not report having DM: data from the National Health and Nutrition Examination Survey showed, based on laboratory results, undiagnosed DM was seen in 3.4% of all US adults and they represented 23% of all adults with DM.⁷⁸

The study was done on a cohort of patients who all had periodontitis. The presence of periodontal disease may have introduced a potential confounding factor that could influence the association between DM and the prevalence of endodontically treated teeth. This may limit the generalizability of the findings to non-periodontitis patients.

Lastly, it remains unclear whether patients were diagnosed with DM prior to experiencing tooth loss or extensive tooth decay, which has resulted in endodontic pathology. In addition, some instances of deep caries may lead to placement of deep restorations or crowns without endodontic treatment.

Recommendations for future research

In future studies on DM versus non-DM, incorporating actual HbAlc values, the DM type, the moment of DM diagnosis, and patient status could inform on DM type as an etiological factor in the prevalence of endodontic treatment. In future analysis, it would also be desirable to consider the distinction between the two types of DM and their status. Based on a recent SR, there is moderate certainty for a higher DMF index score in DM patients compared to those without DM.⁸ Difference between DM types may be the cause for apical pathophysiology resulting from extensive caries lesions reaching into the pulp, ^{59,79} which would be an interesting line of further research.

CONCLUSION

In the matched patient sample diagnosed with adult periodontitis, there was no significant association between DM and the number of endodontically treated teeth or loss of teeth. This suggests that in periodontitis patients DM is not a risk factor influencing the degree of tooth decay necessitating endodontic intervention, nor does it seem to contribute to an increased likelihood of tooth loss in this context.

CLINICAL RELEVANCE

Background

The bidirectional relationship between diabetes mellitus (DM) and periodontal disease is well-documented. However, less is known about DM as a disease-modifying factor in the progression of caries lesions and the incidence of apical periodontitis (AP). Emerging evidence suggests a potential association between AP and DM. Given this increased risk, it is pertinent to explore whether this predisposition translates into a higher prevalence of endodontic treatments.

Added value of this study

This retrospective case-control analysis of periodontitis patients includes a well-matched sample of individuals with and without DM, matched by age and gender. With a robust sample size of over 450 cases and controls, the study achieves strong statistical power. Potential confounders, such as the percentage of sites with pocket depths >5 mm and smoking status, were controlled for, providing a reliable estimate of differences in the number of endodontically treated teeth between the groups.

Clinical implications

The findings indicate that, among periodontitis patients, DM is not associated with an increased number of endodontic treatments.

Online Appendices



STATEMENTS

Acknowledgements

The authors are grateful to Mirella Rijnen, Hannie Ribbink and the other employees of the Paro Praktijk Utrecht for their time and effort during the days we visited the clinic for data extraction. Also, David Alexander is acknowledged for his help for the correct use of the English language.

Statement of ethics

Approval by an Institutional Review Board for Human Research was not required. The institutional review board of ACTA approved the protocol of this retrospective analysis under reference number 2021-11526.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Funding sources

G.A. Van der Weijden was the founder and until recently held a minority interest in the Clinic for Periodontology Utrecht, The Netherlands. This research did not receive any specific grant from funding agencies in the public, commercial, or non-for-profit sectors. This retrospective analysis was self-funded by the authors and their respective institutions as work for this paper is funded by a regular academic appointment at the ACTA of Slot, Van der Weijden and Weijdijk.

Author contributions

LPMW: contributed to conception and design, collected the data, analyzed the data, and drafted the manuscript.

DES: contributed to conception and design, analyzed the data, and critically revised the manuscript.

MK; collected the data and analyzed the data and drafted the initial manuscript.

GAW: contributed to conception and design, analyzed the data, and critically revised the manuscript.

All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Data availability statement

All data generated or analyzed during this retrospective analysis are included in this article and the onlince appendices. Further enquiries can be directed to the corresponding author.

REFERENCES

- World Health Organization. Diabetes . November 14, 2024. Accessed January 7, 2025. https://www.who.int/news-room/fact-sheets/detail/diabetes
- 2. Zaccardi F, Webb DR, Yates T, Davies M. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. Postgrad Med J. 2016;92:63-69. doi:10.1136/postgradmedj-2015-133281
- 3. International Diabetes Federation. *IDF Diabetes Atlas.* 10th ed.; 2021. Accessed March 7, 2025. https://www.diabetesatlas.org
- 4. Chapple IL, Genco R. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol.* 2013;84:S106-S112. doi:10.1902/JOP.2013.1340011
- 5. GBD 2017 Oral Disorders Collaborator, Bernabe E, Marcenes W, et al. Global, Regional, and National Levels and Trends in Burden of Oral Conditions from 1990 to 2017: A Systematic Analysis for the Global Burden of Disease 2017 Study. *J Dent Res.* 2020;99:362–373.
- 6. Tu C, Wang G, Hu Z, Wang S, Yan Q, Liu X. Burden of oral disorders, 1990–2019: estimates from the Global Burden of Disease Study 2019. *Archives of Medical Science*. 2023;19:930–940. doi:10.5114/aoms/165962
- 7. Zhou G, Shu X, Long Y, et al. Dental caries and salivary alterations in patients with type 2 diabetes: A systematic review and meta-analysis. *J Dent.* 2024;150. doi:10.1016/j.jdent.2024.105321
- 8. LPM Weijdijk, GA van der Weijden, DE Slot. DMF scores in patients with diabetes: a systematic review and meta-analysis of observational studies. *J Dent.* 2023;136:1-13. doi:10.1016/j.jdent.2023.104628.
- 9. Ziukaite L, Slot DE, van der Weijden FA. Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies. *J Clin Periodontol*. 2018;45(6):650-662. doi:10.1111/jcpe.12839
- 10. Ong G. Periodontal disease and tooth loss. Int Dent J. 1998;48(\$3):233-238. doi:0.1111/j.1875-595x.1998.tb00711.x.
- 11. Weijdijk LPM, Ziukaite L, Van der Weijden GA, Bakker E, Slot DE. The risk of tooth loss in patients with diabetes: a systematic review and meta analysis . *Int J Dent Hyg.* 2022;20(1):145-166. doi:10.1111/idh.12512
- 12. Cabanillas-Balsera D, Martín-González J, Montero-Miralles P, Sánchez-Domínguez B, Jiménez-Sánchez MC, Segura-Egea JJ. Association between diabetes and nonretention of root filled teeth: a systematic review and meta-analysis. *Int Endod J.* 2019;52(3):297-306. doi:10.1111/iej.13011
- 13. Liu X, He G, Qiu Z, et al. Diabetes Mellitus Increases the Risk of Apical Periodontitis in Endodontically-Treated Teeth: A Meta-Analysis from 15 Studies. *J Endod*. 2023;49(12):1605-1616. doi:10.1016/j.joen.2023.07.016
- 14. Paljević E, Brekalo Pršo I, Vidas Hrstić J, Božac E, Pezelj-Ribarić S, Peršić Bukmir R. Healing of apical periodontitis in type II diabetes mellitus patients: A prospective study. *Oral Dis.* 2024;30(5):3422-3420. doi:10.1111/odi.14772
- 15. Segura-Egea JJ, Martín-González J, Cabanillas-Balsera D, Fouad AF, Velasco-Ortega E, López-López J. Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis. *Clin Oral Investia*. 2016;20(6):1133-1141. doi:10.1007/s00784-016-1805-4
- 16. Viswanath B, Priyank H, Shivakumar S, et al. Periapical healing outcome following non-surgical endodontic intervention among diabetic patients: A systematic review conducted according to PRISMA guidelines and the Cochrane handbook for systematic reviews of interventions. Saudi Dental Journal. 2024;36(1):52-59. doi:10.1016/j. sdentj.2023.10.002
- 17. Chung YL, Lee JJ, Chien HH, Chang MC, Jeng JH. Interplay between diabetes mellitus and periodontal/pulpal-periapical diseases. *J Dent Sci.* 2024;19(3):1338-1347. doi:10.1016/j.jds.2024.03.021
- 18. Pimenta RMN, dos Reis-Prado AH, de Castro Oliveira S, et al. Effects of diabetes mellitus on dental pulp: A systematic review of in vivo and in vitro studies. *Oral Dis.* 2024;(2):100-115. doi:10.1111/odi.14267
- 19. Segura-Egea J, Castellanos-Cosano L, Machuca G, et al. Diabetes mellitus, periapical inflammation and endodontic treatment outcome. *Med Oral Patol Oral Cir Bucal.* 2012;17(2):356. doi:0.4317/medoral.17452.
- 20. Bender IB, Seltzer S, Freedland J. The relationship of systemic diseases to endodontic failures and treatment procedures. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 1963;16(9):1102-1115. doi:doi:10.1016/0030-4220(63)90226-3.
- 21. Segura-Egea JJ, Martín-González J, Castellanos-Cosano L. Endodontic medicine: Connections between apical periodontitis and systemic diseases. *Int Endod J.* 2015;48(10):933-951. doi:10.1111/iej.12507
- 22. Gorni FG, Gagliani MM. The outcome of endodontic retreatment: a 2-yr follow-up. *J Endod.* 2004;30(1):1-4. doi:10.1097/00004770-200401000-00001.
- 23. Friedman S, Mor C. The success of endodontic therapy—healing and functionality. *Calif Dent Assoc.* 2004;32(6):493–503.
- 24. Siqueira JF, Rôças IN. Present status and future directions in endodontic microbiology. *Endod Topics*. 2014;30(1):3-22. doi:10.1111/etp.12060
- 25. Guerrero-Gironés J, Ros-Valverde A, Pecci-Lloret MP, Pecci-Lloret MR, Rodríguez-Lozano FJ. Association between pulpal-periapical pathology and autoimmune diseases: A systematic review. *J Clin Med.* 2021;10(21):4886. doi:10.3390/jcm10214886
- 26. Camponogara JG, Ferreira T de GM, Pelissari TR, Anversa AM, Moreira CHC, Bier CAS. Demographics, smoking status, and systemic health factors associated with apical periodontitis in a Brazilian rural population: a cross-

- sectional study. Clin Oral Investig. 2023;27:7319-7325. doi:10.21203/rs.3.rs-2954226/vl
- 27. Heikkilä P, Niskanen L, But A, Sorsa T, Haukka J. Oral health associated with incident diabetes but not other chronic diseases: A register-based cohort study. *Front Oral Health*. 2022;3:956072. doi:0.3389/froh.2022.956072.
- 28. Strother KK, Kookal KK, Bueso V, Walji MF, Letra A. Association Between Diabetes Mellitus and Endodontic Pathosis. Published online August 21, 2023. doi:10.1101/2023.08.16.23294173
- 29. Ruiz XF, Duran-Sindreu F, Shemesh H, et al. Development of Periapical Lesions in Endodontically Treated Teeth with and without Periodontal Involvement: A Retrospective Cohort Study. *J Endod.* 2017;43(8):1246-1249. doi:10.1016/j. ioen.2017.03.037.
- 30. Langeland K, Rodrigues H, Dowden W. Periodontal disease, bacteria, and pulpal histopathology. *Oral Surg Oral Med Oral Pathol.* 1974;37(2):257-270. doi:10.1016/0030-4220(74)90421-6.
- 31. Zehnder M, Gold SI, Hasselgren G. Pathologic interactions in pulpal and periodontal tissues. *J Clin Periodontol.* 2002;29(8):663-671. doi:10.1034/j.1600-051X.2002.290801.x
- 32. Jansson L. Relationship between apical periodontitis and marginal bone loss at individual level from a general population. *Int Dent J.* 2015;65(2):71-76. doi:10.1111/idi.12143
- 33. Jansson L, Ehnevid H. The Influence of Endodontic Infection on Periodontal Status in Mandibular Molars. *J Periodontol.* 1998;69:1392-1396. doi:10.1902/jop.1998.69.12.1392.
- 34. Jansson L, Lidskog HS, Blomiof L. The influence of endodontic infection on progression of marginal bone loss in periodontitis. *J Clin Periodoniol*. 1995;22:729–734.
- 35. Stassen IGK, Hommez GMG, De Bruyn H, De Moor RJG. The relation between apical periodontitis and root-filled teeth in patients with periodontal treatment need. Int Endod J. 2006;39(4):299–308. doi:10.1111/j.1365-2591.2006.01098.x
- 36. Bender IB, Bender AB. Diabetes mellitus and the dental pulp. *J Endod.* 2003;29(6):383-389. doi:10.1097/00004770-200306000-00001.
- 37. Singh I, Singh P, Singh A, Singh T, Kour R. Diabetes an inducing factor for dental caries: A case control analysis in Jammu. *J Int Soc Prev Community Dent.* 2016;6(2):125-129. doi:10.4103/2231-0762.178748
- 38. Bergenholtz G, Cox CF, Loesche WJ, Syed SA. Bacterial leakage around dental restorations: its effect on the dental pulp. *J Oral Pathol.* 1982;11(6):439-450. doi:10.1111/j.1600-0714.1982.tb00188.x.
- 39. León-López M, Cabanillas-Balsera D, Martín-González J, et al. Does Diabetes Increase the Frequency of Root-Filled teeth: Systematic Review and Meta-Analysis of Observational Studies. *J Clin Exp Dent.* 2023;15(11):e945-e953. doi:10.4317/jced.61011
- 40. López-López J, Jané-Salas E, Estrugo-Devesa A, Velasco-Ortega E, Martín-González J, Segura-Egea JJ. Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: a cross-sectional study. *J Endod.* 2011;37(5):598-601. doi:10.1016/j.joen.2011.01.002.
- 41. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-349. doi:10.1016/j.jclinepi.2007.11.008.
- 42. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg.* 2014;12(12):1500-1524. doi:10.1371/journal.pmed.0040297.
- 43. Benchimol El, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med.* 2015;12(10). doi:10.1371/journal.pmed.1001885.
- 44. CCMO: Central Committee on Research Involving Human Subjects. Accessed March 7, 2025. https://english.ccmo.nl/.
- 45. American Dental Association. Dental Radiographic examinations: recommendations for patient selection and limiting radiation exposure. 2012. Accessed March 7, 2025. https://www.fda.gov/radiation-emitting-products/medical-x-ray-imaging/selection-patients-dental-radiographic-examinations
- 46. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. In: *Journal of Clinical Periodontology.* Vol 45. Blackwell Munksgaard; 2018:S162–S170. doi:10.1111/jcpe.12946
- 47. van der Velden U. Purpose and problems of periodontal disease classification. *Periodontol 2000.* 2005;39:13-21. doi:10.1111/j.1600-0757.2005.00127.x.
- 48. van der Velden U. Diagnosis of periodontitis. *J Clin Periodontol*. 2000;27(12):960-961. doi:10.1034/j.1600-051x.2000.027012960.x
- 49. Ziukaite L, Slot DE, Cobb CM, Coucke W, van der Weijden GA. Prevalence of diabetes among patients diagnosed with periodontitis: A retrospective cross-sectional study. *Int J Dent Hyg.* 2017;16(2):305-311. doi:10.1111/idh.12280.
- 50. Poyato-Borrego M, Segura-Sampedro JJ, Martín-González J, Torres-Domínguez Y, Velasco-Ortega E, Segura-Egea JJ. High Prevalence of Apical Periodontitis in Patients with Inflammatory Bowel Disease: An Age-and Gender-matched Case-control Study. *Inflamm Bowel Dis.* 2020;26(2):273-279. doi:10.1093/ibd/izz128
- 51. Van der Weijden GA, Dekkers GJ, Slot DE. Success of non-surgical periodontal therapy in adult periodontitis patients: A retrospective analysis. *Int J Dent Hyg.* 2019;17(4):309–317. doi:10.1111/idh.12399
- 52. Chen H, Cohen P, Chen S. How Big is a Big Odds Ratio? Interpreting the Magnitudes of Odds Ratios in Epidemiological Studies. Communications in Statistics—simulation and Computation®. 2010;39(4):860-864.

- 53. Oyetola EO, Adesina OM, Ogunbameru K, Egunjobi S, Adejobi AF. Distribution of Medical Conditions among Dental Patients. *Nigerian Medical Journal*. 2020;61(3):129-135. doi:10.4103/nmj.NMJ 80 19.
- 54. Chapple ILC, Bouchard P, Cagetti MG, et al. Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. *J Clin Periodontol.* 2017;44:S39–S51. doi:10.1111/jcpe.12685
- 55. Marotta PS, Fontes TV, Armada L, Lima KC, Rôças IN, Siqueira Jr. JF. Type 2 diabetes mellitus and the prevalence of apical periodontitis and endodontic treatment in an adult Brazilian population. *J Endod.* 2012;38(3):297-300. doi:10.1016/j.joen.2011.11.001.
- 56. Arya S, Duhan J, Tewari S, Sangwan P, Ghalaut V, Aggarwal S. Healing of Apical Periodontitis after Nonsurgical Treatment in Patients with Type 2 Diabetes. *J Endod.* 2017;43(10):1623-1627. doi:10.1016/j.joen.2017.05.013
- 57. Rudranaik S, Nayak M, Babshet M. Periapical healing outcome following single visit endodontic treatment in patients with type 2 diabetes mellitus. *J Clin Exp Dent*. 2016;8(5):e498-e504. doi:10.4317/jced.52859
- 58. Malvania EA, Sheth SA, Sharma AS, Mansuri S, Shaikh F, Sahani S. Dental caries prevalence among type II diabetic and nondiabetic adults attending a hospital. *J Int Soc Prev Community Dent.* 2016;6(3):232-236. doi:10.4103/2231-0762197202
- 59. Sampaio N, Mello S, Alves C. Dental caries-associated risk factors and type 1 diabetes mellitus. *Pediatr Endocrinol Diabetes Metab.* 2011;17(3):152-157.
- 60. Sabharwal A, Stellrecht E, Scannapieco FA. Associations between dental caries and systemic diseases: a scoping review. *BMC Oral Health*. 2021;21(1):472. doi:10.1186/s12903-021-01803-w.
- 61. Segura-Egea JJ, Martín-González J, Cabanillas-Balsera D, Fouad AF, Velasco-Ortega E, López-López J. Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis. *Clin Oral Investig.* 2016;20(6):1133-1141. doi:10.1007/s00784-016-1805-4
- 62. Aminoshariae A, Kulild JC, Mickel A, Fouad AF. Association between systemic diseases and endodontic outcome: a systematic review. *J Endod.* 2017;43(4):514–519. doi:10.1016/j.joen.2016.11.008.
- 63. Tibúrcio-Machado CS, Michelon C, Zanatta FB, Gomes MS, Marin JA, Bier CA. The global prevalence of apical periodontitis: a systematic review and meta-analysis. *Int Endod J.* 2021;54(5):712-735. doi:10.1111/iej.13467
- 64. Segura-Egea JJ, Jiménez-Pinzón A, Ríos-Santos JV, Velasco-Ortega E, Cisneros-Cabello R, Poyato-Ferrera M. High prevalence of apical periodontitis amongst type 2 diabetic patients. *Int Endod J.* 2005;38(8):564-569. doi:10.1111/j.1365-2591.2005.00996.x.
- 65. Salehrabi R, Rotstein I. Endodontic treatment outcomes in a large patient population in the USA: an epidemiological study. *J Endod*. 2004;30:346–350. doi:10.1097/01.don.0000145031.04236.ca.
- Zadik Y, Sandler V, Bechor R, Salehrabi R. Analysis of factors related to extraction of endodontically treated teeth. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 2008;106(5). doi:10.1016/j. tripleo.2008.06.017
- Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. Commun Stat Theory Methods. 2017;46(14):6774-6781. doi:10.1080/03610926.2015.1134575
- 68. Simpson TC, Clarkson JE, Worthington HV, et al. Treatment of periodontitis for glycaemic control in people with diabetes mellitus. *Cochrane Database Syst Rev.* 2022;4:CD004714. doi:10.1002/14651858.CD004714.pub4.
- 69. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol.* 2013;84(4):106-112.
- 70. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Clin Periodontol*. 2018;45:S149–S161. doi:10.1111/jcpe.12945
- 71. Balto HA, Alabdulaaly L, Bahammam S, Al-Ekrish AA. Comparative analysis of prevalence of apical periodontitis in smokers and non-smokers using cone-beam computed tomography. Saudi Dental Journal. 2019;31(1):52-57. doi:10.1016/j.sdentj.2018.09.006
- 72. Rodriguez FR, Taner B, Weiger R, Walter C. Is smoking a predictor of apical periodontitis? *Clin Oral Investig.* 2013;17(8):1947-1955. doi:10.1007/s00784-012-0893-z
- 73. Correia-Sousa J, Madureira AR, Carvalho MF, Teles AM, Pina-Vaz I. Apical periodontitis and related risk factors: Cross-sectional study. *Revista Portuguesa de Estomatologia, Medicina Dentaria e Cirurgia Maxilofacial.* 2015;56(4):226-232. doi:10.1016/j.rpemd.2015.08.004
- 74. Cabanillas-Balsera D, Segura-Egea JJ, Jiménez-Sánchez MC, et al. Cigarette smoking and root filled teeth extraction: Systematic review and meta-analysis. *J Clin Med.* 2020;9(10):1-13. doi:10.3390/jcm9103179
- 75. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol*. 2004;57(10):1096-1103. doi:10.1016/j.jclinepi.2004.04.005
- 76. Martin LM, Leff M, Calonge N, Garrett C, Nelson DE. Validation of Self-Reported Chronic Conditions and Health Services in a Managed Care Population. *Am J Prev Med.* 2000;3(18):215-218. doi:10.1016/s0749-3797(99)00158-0.
- 77. Althubaiti A. Information bias in health research: Definition, pitfalls, and adjustment methods. *J Multidiscip Healthc.* 2016;9:211-217. doi:10.2147/JMDH.S104807
- 78. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Centers for Disease Control and Prevention (CDC). Hyattsville, MD: U.S. Department of Health and Human Services, Centers

- for Disease Control and Prevention. September 26, 2022. Accessed March 7, 2025. https://www.cdc.gov/nchs/nhanes/index.htm
- 79. Patiño Marin N, Loyola Rodríguez JP, Medina Solis SE, Pontigo LA, Reyes MJ, Ortega RJ. Caries, periodontal disease and tooth loss in patients with diabetes mellitus types 1 and 2. *Acta Odontol Latinoam*. 2007;21(2):127-133.

"If you can't stand the heat, get out of the kitchen"

Gordon Ramsay

CHAPTER EIGHT

The risk of tooth loss in patients with diabetes

A systematic review and meta-analysis

L.P.M. Weijdijk, L. Ziukaite, G.A. Van der Weijden, E. Bakker, D.E. Slot *International Journal Dental Hygiene.* 2022;20(1):145-166.



ABSTRACT

Objective

The aim of this systematic review was to comprehensively and critically summarize and synthesize the risk of losing teeth among with diabetes mellitus (DM) compared to those without DM, as established in observational studies.

Methods

MEDLINE-PubMed and Cochrane databases were searched through a period from their inception through October 2020 to identify eligible studies. Papers that primarily evaluate the number of teeth in DM patients compared to non-DM individuals were included. A descriptive analysis of the selected studies was conducted, and when feasible, a meta-analysis was performed. The quality of the studies was assessed.

Results

A total of 1087 references were generated, and screening of the papers resulted in 10 eligible publications. A descriptive analysis demonstrated that six of these studies indicate a significantly higher risk of tooth loss in DM patients. This was confirmed by the meta-analysis risk ratio of 1.63 95% CI (1.33; 2.00, p<0.00001). Subgroup analysis illustrates that this is irrespective of the risk-of-bias assessment. The higher risk of tooth loss in DM patients was also higher when only DM type II patients or studies with a cross-sectional design were considered. Patients with a poor DM control status presented a significantly increased risk of tooth loss. When the data were separated by the world continent where the study was performed, Asia and South America had numerically higher risks and a 95% CI that did not overlap with Europe and North America.

Conclusion

There is moderate certainty for a small but significantly higher risk of tooth loss in DM patients as compared to those without DM.

INTRODUCTION

Tooth loss considerably affects oral health–related quality of life (OHRQoL), causing chewing difficulty, poor dietary intake and functional disorders.¹ A predominant reason for tooth loss is periodontitis, which is an inflammation of periodontal tissues. Damage from periodontal disease can lead to loosening of teeth and, in a final stage, to tooth loss.².³ The manifestation and progression are influenced by a wide variety of determinants and factors that have been linked with general health. Notably, the association between periodontitis and diabetes mellitus (DM) has been highlighted in the literature. Periodontal disease is considered the sixth complication of DM.⁴ Another primary cause of tooth loss is dental caries. Its development of which is presumably enhanced in DM patients.⁵.6

Due to the ageing population, DM is a growing public health problem, and it likely contributes to a greater demand for health care. The negative effects of elevated blood sugars on the immune system result in an increased susceptibility to infections. The risk for development and progression of periodontitis is increased approximately threefold in DM patients as compared to non-diabetic individuals (non-DM). Furthermore, DM is associated with increased severity of periodontal disease. The increased risk of dental caries in DM patients can likely be explained by decreased salivary flow rates and expanded levels of glucose in the saliva. The American Diabetes Association and International Diabetes Federation have published DM care guidelines, the main goal is prevention and treatment of DM complications, thereby optimizing quality of life (QoL).

Periodontal pocket depth and clinical attachment loss are commonly utilized to define a patient with periodontitis. However, these outcome measurements are surrogate endpoints of disease. A true endpoint (e.g., tooth loss) would directly assess patients' experience on the onset of periodontitis. Moreover, tooth loss also affects QoL. A recent systematic review (SR) and meta-analysis assesses predictors of tooth loss, including DM, in periodontitis patients. However, no SR with a specific focus on the risk of tooth loss in DM patients has yet been performed. In the light of the increasingly available evidence, the aim of this SR is to comprehensively and critically summarize and synthesize the available scientific evidence emerging from observational studies on the number of teeth among DM patients as compared to non-DM patients.

METHODS

The preparation and presentation of this SR is in accordance with the *Cochrane Handbook for Systematic Reviews*¹⁷ and the guideline for Meta-Analysis of Observational Studies in Epidemiology (MOOSE).¹⁸ A protocol was developed a priori following the initial discussion between the members of the research team. This study is registered at the ACTA University institutional review board by number 2021-71228.

Focused question

A precise review question was formulated utilizing the population, exposure, comparison, outcomes and study (PECOS)¹⁹ framework as follows:

- Is there a higher risk, loosing teeth among patients with DM compared to those without DM, as it was established in observational studies?
- Due do a potential link between DM and both caries and periodontitis, it is hypothesized that DM patients are at higher risk, loosing teeth.

Search strategy

A structured search strategy was designed to retrieve all relevant studies that evaluate the number of missing teeth among patients with DM as compared to non-DM individuals. After consultation with a clinical librarian, the search was designed by two reviewers (LPMW and DES). The National Library of Medicine in Washington, DC (MEDLINE-PubMed), and Cochrane Central were searched from the inception of this study through October 2020 for appropriate papers that answer the focused question. Table 1 provides details regarding the search approach employed. For the search, no limitation was applied on language or date of publication.

The reference lists of the studies included in this review were hand-searched to identify additional potentially relevant studies. Moreover, national (http://www.trialregister.nl) and international trial registries (http://apps.who.int/trialsearch, http://www.ClinicalTrials.gov) were searched for relevant unpublished or ongoing studies. Furthermore, the following database sources were searched for possible relevant studies that have not reached full publications: OpenGrey (http://www.opengrey.eu/), British Library Inside(http://www.bl.uk/ inside), the European Federation of Periodontology (http://www.epf.net), the International Association for Dental Research (http://www.iadr.org), Web of Science, BIOSIS Previews and OVID (http://www.ovid.com). The conference proceedings of the International Association for Dental Research and the European Organization for Caries Research were searched through October 2020. Additionally, the previous 12 months of the following journals were handsearched to eliminate potential delay in indexing journals at the National Library of Medicine: Journal of Operative Dentistry, Journal of Clinical Dentistry, Journal of Dental Research, Journal of Caries Research, International Journal of Dental Hygiene, The Journal of Dental Hygiene, Journal of Clinical Periodontology, The Journal of Periodontology, Periodontology 2000, Oral Health and Preventive Dentistry.

Table 1

Search terms used for PubMed-MEDLINE. The search strategy was customized according to the database being searched.

{[<exposure>] AND [<outcome>]}

<Exposure>

("diabetes mellitus" [Mesh] OR diabetes OR (diabetes mellitus)[textwords])]

AND

<Outcome:>

(tooth loss) OR (toothloss) OR (teeth loss) OR (teethloss) OR (teethless) OR (toothless) OR (missing teeth) OR (missing tooth) OR (loss of teeth) OR (loss of tooth) OR (number of teeth) OR number of tooth))))) OR tooth loss [MeSH Terms]))]}

The asterisk (*) was used as a truncation symbol

Screening and selection

A two-stage, electronic data search and selection was performed. First, titles and abstracts (when available) of all studies identified through the searches were screened. Second, details of the selected studies that potentially met the inclusion criteria were further assessed. This process was independently performed by two reviewers (LPMW and DES). If the information relevant to the screening criteria was not available in the title or abstract, or if the full text was not retrievable, then the paper was excluded.

Predetermined inclusion criteria for the first screening of titles and abstract were as follows:

- Mentioned in the aim or title of the study:
 - The number of teeth present, tooth loss, missing teeth, extracted teeth, Decayed Missed Filled Teeth (DMFT number).
- DM or any other synonym, such as impaired glucose tolerance, glucose metabolism, glycemic control or metabolic syndrome, as a single disease (no comorbidities by other systemic diseases).
 - Participants were ≥ 18 years old.

After this phase, full-text versions were obtained. For the studies that appeared to meet the first set of screening criteria or for which the title and abstract provided insufficient information to make a clear decision, full-text papers were retrieved. These were read independently by the two review authors, LPMW and DES.

A full-text review of all the pertinent articles was completed utilizing the following eligibility criteria:

- Full-text paper available in English.
- Observational studies: cohort, case-controlled or cross-sectional studies. Data should be presented as a cross-sectional design.
- Studies conducted with human subjects who were:
 - ≥ 18 years.
 - In satisfactory general health (no systemic disorders or comorbidities).
 - Evaluating a group of patients with DM as well as a group of people without DM.
- DM status:
 - Either self-reported or clinically assessed.
 - Type of DM: undefined, type I and/or type II. Prediabetes and gestational DM were excluded.

- Reported outcomes:
 - Based on a full-mouth assessment.
 - Clinically determined number of teeth (no radiographs).
 - Number of missing teeth or number of teeth present as an absolute number of teeth or as a population mean.
 - Tooth loss presented as cross-sectional data for an individual over the lifetime until the moment of assessment (not for the duration of a specific period).

Any disagreement between the two reviewers about the eligibility of studies was resolved after additional discussion. If disagreement persisted, a third reviewer, GAW, was consulted, whose judgment was considered to be decisive. Thereafter, the selected full-text papers that fulfilled all eligibility criteria were identified and included in this SR for data extraction and estimation of the risk of bias. At this stage, the reasons for exclusion were recorded (see Online Appendix S1).

Methodological quality assessment

Two reviewers (LPMW and DES) independently scored the individual methodological qualities of the included studies utilizing the risk of bias in observational studies of exposures (ROBINS-E) instrument. This tool assesses risk of bias in non-randomized studies of exposures and is under development by researchers from University of Bristol (UK), McMaster University (Canada) and the Environmental Protection Agency (USA). The preliminary draft tool version July 2017 was utilized; this instrument is modeled on the risk of bias in non-randomized studies of interventions (ROBINS-I) instrument.²⁰⁻²²

The application of the ROBINS-E tool consists of the following steps:

- Step I: framing the review question, describing potential confounders, co-interventions and exposure and outcome measurement accuracy information.
- Step II: describing each eligible study, including specific confounders and co-interventions for each study.
- Step III: determining risk of bias consideration through seven items regarding the strengths and limitations of studies.

Quality was assigned as low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias or no information with the following domains: bias due to confounding, bias in selection, bias in classification, bias due to departures from intended exposures, bias due to missing data, bias in measurement of outcomes and bias in selection of reported results.

The judgments within each domain are carried forward to an overall risk of bias. A study was classified as having a low risk of bias when all domains were judged to be at low risk of bias. Moderate risk of bias was assigned when, for one or more domains, the study was judged not to be higher than moderate risk of bias. A study was classified as having serious risk of bias when, for one or more domains at the most, serious risk of bias was scored. An overall critical risk of bias was scored when at least one domain was judged to be at critical risk of bias. No information was assigned if the study was judged to be at serious or critical risk of bias and there was a lack of information in one or more key domains.²⁰⁻²²

Data extraction

For those papers that provided insufficient data to be included in the analysis, the first or corresponding authors were contacted by email to query whether additional data could be provided. Independent data extraction was performed by two reviewers (LPMW and DES) utilizing a custom-designed standardized data extraction form. Disagreement between the reviewers was resolved through discussion and consensus. If disagreement persisted, a third reviewer (GAW) was consulted; this judgment was decisive. Data extraction of all included studies having either an observational, cohort or case-controlled design were approached as cross-sectional studies. From the eligible papers, details on study design, demographics, details of the DM status and number of missing teeth or teeth present was extracted.

The latter was determined by utilizing the following parameters:

- Total number of evaluated teeth, reference point, either 28 (excluding evaluation of wisdom teeth) or 32 (including wisdom teeth) per included study.
- Number of missing teeth, as an absolute number of teeth or as a population mean of tooth loss.
- Number of teeth present, as an absolute number of teeth or as a population mean. If only the number of currently present teeth is provided, then the number of missing teeth was calculated based on the number of evaluated teeth being either 28 or 32 for each participant.
- The DMFT number; data concerning the number of missing teeth were extracted from this parameter.

When an included study provided multiple age groups of individuals 18 years and older, data were merged so that these were considered as one group. If a DM group was specified in the categories of prediabetes and DM, then the prediabetic data was excluded. When DM types I and II are presented separately in the original included papers, these groups were merged for the overall analysis. If possible, a subgroup analysis on DM types I and II was performed if the original group data allowed for separation of these two groups.

Data analysis

Assessment of clinical and methodological heterogeneity

The factors utilized to assess the clinical heterogeneity of the outcomes of the various studies are as follows:

- Characteristics of participants (age, sex and continent)
- Evaluable number of teeth
- DM type: I or I
- Method of assessment (professionally diagnosed or self-reported DM).²³

Factors employed to assess the methodological heterogeneity were study design details and the total number of evaluated teeth, reference point (28 or 32).

When clinical or methodological heterogeneity was presented across studies, sources of heterogeneity were investigated with subgroup or sensitivity analyses.¹⁷

As the total number of evaluable teeth (28 or 32) has a direct influence on the relative ratio of the missing teeth to the total number of teeth, this was defined a priori as a reason for subgroup analysis. Other potentially relevant subgroup analyses were study design (studies originally designed as cross-sectional evaluations), participant demographics, potential risk

of bias and the world continent where the study was performed, and data were obtained. For DM-related details, a sub-analysis was also conducted with respect to DM control (poor or well regulated), insulin dependence (yes or no) and DM duration.

Descriptive methods

As a summary, a descriptive data presentation is utilized for all studies.

Quantitative methods

A meta-analysis was performed comparing the number of missing teeth among patients with DM to those without DM. For a subsequent subgroup analysis, a meta-analysis was performed if more than one study could be included. Analysis was performed utilizing Review Manager version 5.3^{24} according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and MOOSE guidelines 18,25 as well as the Cochrane handbook. 7 From the data, the relative risk or risk ratio (RR) with its associated 95% confidence interval and p-value were calculated for the number of missing teeth among DM patients as compared to non-DM individuals. P-values ≤ 0.05 were considered to be significant.

The absolute number of teeth per group in a study was utilized so that the data were weighed according to the study population. If the absolute numbers were not provided, then the number of teeth for the entire group was calculated based on the population mean multiplied by the number of participants in each group (DM or non-DM). The RR between DM patients and non-DM individuals was calculated utilizing both random- and fixed-effects models where appropriate. When there was heterogeneity that could not readily be explained, the analytical approach was conducted according to a random-effects model. If there were less than four studies, then a fixed-effects analysis was performed because it may be impossible to estimate the between-study variance with any precision. In such a case, the fixed-effects model is the only option.¹⁷

It was expected that there would be considerable heterogeneity among the included studies, as study designs and details presumably differ. Moreover, DM is not likely to be the single cause for tooth loss. Clinically, DM can vary in its features, which is likely and was the case in the DM population of the included studies. This variance was considered by primarily utilizing the random-effects model, the exception being when less than four studies were eligible for meta- analysis. Otherwise, the fixed-effects model was utilized, as advised by the Cochrane Oral health group.²⁶

Sensitivity analyses were undertaken to evaluate the effect of excluding studies based on specific aspects in the domain of clinical or methodological heterogeneity. The testing for publication bias per outcome was utilized as proposed by Egger et al.²⁷ If the meta-analysis involved a sufficient number of trials to make visual inspection of the funnel plot meaningful (a minimum of 10 trials), then these plots were employed as tools to assess publication bias. The presence of asymmetry in the inverted funnel is suggestive of publication bias.^{17,25}

Assessment of statistical heterogeneity

Statistically, heterogeneity was tested by the chi-square test and l^2 statistic. A chi-square test resulting in a p<0.1 was considered an indication of significant statistical heterogeneity. As a rough guide to assess the possible magnitude of inconsistency across studies, an l^2 statistic of 0%-40% was interpreted to indicate unimportant levels of heterogeneity. An l^2

statistic of 30%–60% may represent moderate heterogeneity, and l^2 statistic of 50%–90% may represent substantial heterogeneity. An l^2 statistic of greater than 75% was interpreted to indicate considerable heterogeneity and was further assessed with subgroup or sensitivity analysis. 28,29

Grading the body of evidence

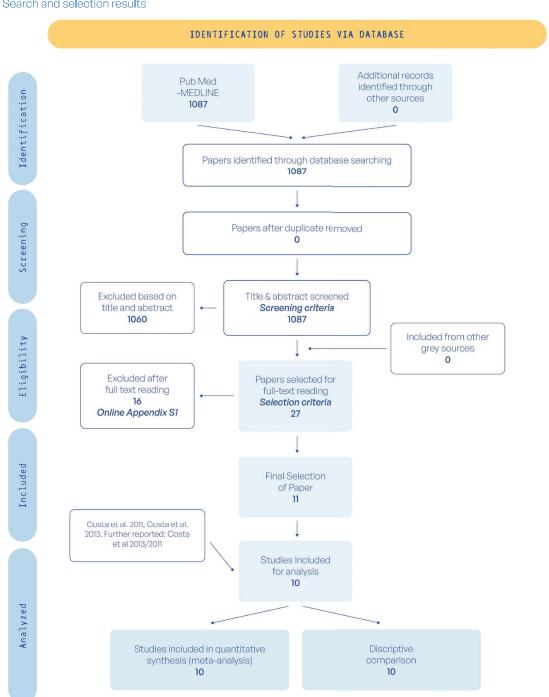
Two reviewers (LPMW and DES) rated the quality of the evidence and the strength of the recommendations according to the following aspects: study limitations, inconsistency of results, indirectness of evidence, imprecision and publication bias by utilizing the Grading of Recommendations Assessment, Development and Evaluation (GRADE),^{30,31} which provides a systematic approach for considering and reporting each of these factors. An overall rating of confidence in effect estimates was considered critical for the final recommendation.³² Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, then the judgement of a third reviewer (GAW) was decisive.

RESULTS

Search and selection process

Searching the MEDLINE-PubMed and Cochrane databases resulted in 1087 unique papers, as Figure 1 illustrates. The first screening of the titles and abstracts resulted in 27 papers for which the full papers were obtained. In the second phase, after full-text reading and contact with the corresponding authors, 16 studies were excluded because they did not meet all items of the eligibility criteria.

Figure 1
Search and selection results



The reasons for which are presented in Online Appendix S1. Three papers do not provide necessary data regarding the overall number of missing teeth, and after contacting the authors, this information could not be retrieved (Wiener et al 2017,³³ Kapp et al 2007,³⁴ Jung et al 2010).³⁵ Oliver and Tervonen 1993)³⁶ performed only half-mouth assessments. Three papers that present the number of missing teeth over a period of time were not included (Yoo et al 2019,³⁷ Mayard-Pons et al 2015³⁸ and Jimenez et al 2012).³⁹ Other reasons for exclusion are found in the table in Online Appendix S1. Hand-searching of the reference list did not reveal any additional papers. Consequently, 11 papers were identified which presented 10 different studies, as data from the paper of Costa et al (2013)⁴⁰ and Costa et al (2011)⁴¹ concern the same study population.

Assessment of clinical heterogeneity

Considerable heterogeneity was observed among the 10 included studies. Characteristics of study design, study population and diagnostic as well as assessment methods are presented in Table 2. The total number of subjects included in this SR is 29.278, which varies from 92 enrolled participants in Study III⁴⁰ to 12.131 in Study I.⁴² The female sex is more prevalent in seven studies (I, II, IV, VI, VII, VIII and X), and two studies include more males (V and IX).

One case-control study makes an effort to match the sex distribution (III). The population in Study II⁴³ is a specific ethnic group (Hispanics or Latinos). Studies originating from the following world continents are present: Europe (VII⁴⁴, IX⁴⁵ and X⁴⁶), North America (III⁴³, IV⁴⁷, and VIII⁴⁸), Asia (I⁴² and VI⁴⁹) and South America (III⁴⁰ and V⁵⁰). All studies include a non-DM group in satisfactory general health who were drawn from the population of the country where the study was performed. The DM participants in Studies IX⁴⁵ and X⁴⁶ were specifically selected from a central hospital or institute for metabolic diseases. For inclusion in the individual studies, criteria and diagnoses were utilized regarding DM status: self-reported (IV⁴⁷) and clinically assessed DM (I⁴², II⁴³, III⁴⁰, V⁵⁰, VII⁴⁹, VIII⁴⁸ and IX⁴⁵). The clinical assessments were performed by different methods, such as fasting plasma glucose (FPG), glucose or HbA1c levels. Study VII⁴⁴ reports DM based on both clinical assessments and self-reports. In one paper, it was unclear how the DM status had been assessed (X).⁴⁶

In total, three studies specifically focus on DM type II (I^{42} , III 40 and VIII 48). One paper differentiates between types I and II (VII 44). For the overall calculations, data from these groups were merged, while for the subgroup analysis, the original group data were employed. Originally, study VIII48 made this distinction, but as the type I DM group included children, this group was consequently excluded from data extraction and only the data on type II DM patients were utilized. Two studies (III 43 and III 40) report data on the DM group about well- and poorly controlled individuals. Smokers among non-DM individuals were separately analyzed in study V 50 , and as none of the DM patients reported smoking, only the non- smoking, non-DM individuals were considered as a control group. Other characteristics concerning DM include short or long duration of DM (I^{46}), insulin independence (I^{45}) and diagnosis of DM known beforehand or assessed on the spot.

 Table 2

 Overview of the studies processed for data extraction

Selection ID	Z	Sexes (N males,	Type of DM	# teeth in patients with	# teeth in people non-DM
study design, country Risk of bias (Online	Type of population	Mean age (SD) Range in years		Total N of teeth used for calculations	Total N of teeth used for calculations
I Shin et al. 2017	Total: 12131 ♦	Total	DM type II	Missing: 7356 ()	Missing: 26331 ()
		♂ 5342 ♦		Total teeth: 36260 ◊	Total teeth: 303408 ◊
Cross-sectional	DM: 1295 ◆	♦ 6289 ♦	Type of assessment:		
Korea	Non-DM: 10836 ◆	Mean age: ?	Prof-D	Patient level:	Patient level:
Rob: Moderate				22,3 T+ ◆	25.6 T+ ◆
	Selected from	DM		5.7 T- ◊	2.4 T- \Diamond
	KNHANES, a study	₫:?			
	periodically conducted	\$:\$		Based on 28 teeth ◆	Based on 28 teeth •
	by the Korea Centre for	Mean age: ?			
	Disease Control and)			
	Prevention (KCDC), in	Non-DM			
	2012-2014.	₫:?			
		<i>:</i> :⇔			
		Mean age: ?			
Il Greenblatt et al.	Total: 9271	Total	DM type I/II	Missing: 10140 (Missing: 20733 (
2016		♂ 6089 ♦		Total teeth: 78176 (Total teeth: 181412 ()
	DM: 2792 (\$ 9043 \(\)	Type of assessment:		
Prospective cohort	Uncontrolled: 1324	Mean age: ? (18-74)	Prof-D	Patient level:	Patient level:
United States	Controlled: 1468			24.4 T+ ◊	24.8 T+ ◊
RoB: Low		DM		3.6 T- ◊	3.2 7-◆
	Non-DM: 6479 ◆	₫:?			
		\$:\$		Based on 28 teeth ◆	Based on 28 teeth ◆
	Hispanic/Latino	Mean age: ?			
	population; from the			Uncontrolled	
	Hispanic	Non-DM		Missing: 5296 ♦	
		₫:?		Total teeth: 37072 ♦	

			Missing: 183 (Total teeth: 1288 ()		Patient level:	24 T+ ◊	4 T- ◊		Based on 28 teeth ◆													
Patient level: 28 T+ ◊ 4 T-◆	Controlled Missing: 4844 • Total teeth: 41104 •	Patient level: 27,7 T+ ◊ 3.3 T- ◆	Missing: 225 (\) Total teeth: 1288 (\)		Patient level:	23.11+ ◊	4.9 T- ◊		Based on 28 teeth ◆	Well controlled	Missing: 96 A	Total teeth: 644 (Patient level:	23,8 T + ♦	7,7 T	Poor controlled	Missing: 129 (Total teeth: 644 (Patient level:	22,4 T+ ()	5,6 T- ()
			DM type II	Type of assessment:	Prof-D																	
♀ ∶? Mean age: ?			Total 3:40	Q :52	Mean age: ? (22-71)		DM	3 20	\$ 26	Mean age: ?		7001 control. 3 10	\$13		Well control:	d 10	<u>∞</u> >+	MC-ncN	o 20	\$ 26	Mean age: ?	
Community Health Study/Study of Latinos (HCHS/SOL).			Total: 92 ♦	DM: 46 ◊	Poorly control: 23 •	Well control: 23 ♦		Non-DM: 46 ◆		Cohort undergoing PMT	-											
			III Costa et al. 2013/2011	•	Case-controlled	Brazil	RoB: Moderate															

3	IV Fatel et al. 2013	101al: 2055 💠	Total ♣ ೧೧၁♠	DM type I/II	Missing: 3763 ()	Missing: 11196 ()
Non-DM: 1671	otional	DM: 384 •	\$ 772 \$ 1063 \$	Type of assessment:		
Non-DM: 1671 ◆ Non-DM: 1671 ◆ Non-DM: 1671 ◆ Non-DM: 1671 ◆ DM	ates		Mean age: ?	Self-R	Patient level:	Patient level:
Caneral population D/M	sno	Non-DM: 1671 ◆)		18.2 T+ ◊	21.3 T+ ◊
Central population d : ?		-	MQ		9.8 7-◆	6.7 T − ♦
Mean age: ? Mean age: 5.4 Mean age: 5.4 Mean age: 5.4 Mean age: 7.2 Mean age		General population	₫:?			
Sample Mean age: ? Non-DM 07:7 9:7 Non-DM O7:7 9:7 Mean age: ? DM type I/II Missing: 481 ◊ O7:67 O7:67 Total DM type I/II Total teeth: 1820 ◊ O7:67 O7:67 Type of assessment: Patient level: 20.6 T + ◊ Non-DM: 59 Selected from the Non-DM School of Dentistry at O7:22 ◊ Type of assessment: DM type I/II Missing: 241 ◊ Total 65		trom the NHANES	¿:•		Based on 28 teeth ♦	Based on 28 teeth ♦
non-DM o:? point q:? Mean age:? DM type I/II Missing: 48I ∳ with DM: 65 ◆ o:57 ∳ Type of assessment: Patient level: 1820 ∳ With DM: 65 ◆ o:57 ∳ Type of assessment: Patient level: 20.6 T+ ∳ Mean age:? Prof-D Patient level: 20.6 T+ ∳ Patient level: 20.6 T+ ∳ Non-DM: 59 ∳ Mean age: 57.4 ∳ Based on 28 teeth ◆ Non-DM: 59 ∳ Mean age: 41.1 ∳ DM type I/II Missing: 24I ∳ Valle Mean age: 72.0 ∳ DM type I/II Missing: 24I ∳ DM: 379 ◆ o 475 ∳ Type of assessment: Patient level: 25.63 T+ ∳ Oeneral population DM Prof-D Prof-D 25.63 T+ ∳ Mining in Nachalasy o 272 ∳ Prof-D Based on 32 teeth ◆ Mining in Nachalasy o 272 ∳ Prof-D Based on 32 teeth ◆		sample	Mean age: ?			
12 Total: 124 ◊ Total DM type I/II Missing: 48I ◊ Men age: ? DM type I/II Missing: 48I ◊ With DM: 65 ◆ \$ -5.5 ↑ Type of assessment: Prof=D Selected from the Non-DM: San Vicente de Paul of 1.45 ◆ Prof=D Prof=D Prof=D Non-DM: 59 ◊ Selected from the School of Dentistry at the Universidad del of 2.22 ⋄ Non-DM Prof=D Pontype I/II Missing: 24l4 ⋄ Valle Mean age: 7(20-86) ◆ Type of assessment: Prof=D Prof=D<			Non-DM			
Total: 124 ⟨⟩ Total			♂ :? O·2			
12 Total DM type I/II Missing: 481 ∮ with DM: 65 ◆ Q: 57 ∮ Type of assessment: Prof-D with DM: 65 ◆ Q: 57 ∮ Type of assessment: Patient level: Selected from the Hospital Universitario DM DM 7.4 T − ∮ San Vicente de Paul (Medellin, Colombia) Q: 20 ◆ 7.4 T − ∮ Non-DM: 59 ∮ Non-DM Bassed on 28 teeth ◆ Non-DM: 59 ∮ Non-DM Bassed on 28 teeth ◆ School of Dentistry at the Universidad del Q: 37 ∮ Non-DM Prof-D Valle Mean age: 7(20-86) ♦ Prof-D Type of assessment: DM: 379 ◆ Q-130 ∮ Type of assessment: Patient level: Non-DM: 22 ∳ Type of assessment: Patient level: 25.63 T + ∮ Non-DM: 22 ∳ Prof-D 25.63 T + ∮ 25.63 T + ∮ Non-DM: 22 ∳ Prof-D 25.63 T + ∮ 25.63 T + ∮ Non-DM: 22 ∳ Prof-D 25.63 T + ∮ 25.63 T + ∮			* . : Mean age: ?			
With DM: ≤5 ◆ Q*: 67 ◊ Type of assessment: Total teeth: 1820 ◊ Selected from the Hospital Universitario Prof-D Prof-D 20.6 T + ◊ Hospital Universitario DM 20.6 T + ◊ 20.6 T + ◊ San Vicente de Paul O: 45 ◆ O: 45 ◆ 20.6 T + ◊ 20.6 T + ◊ Non-DM: San Vicente de Paul O: 20 ◆ Non-DM: 20 ♦ 20.5 T + ◊ 20.5 T + ◊ Non-DM: 59 ◊ Non-DM: 59 ◊ Non-DM: 20 ♦ Non-DM: 20 ♦ Non-DM: 20 ♦ School of Dentistry at O: 20 ♦ Mean age: 57.4 ◊ DM type I/II Missing: 244 ◊ Valle Non-DM: 20 ♦ Type of assessment: Patient level: Non-DM: 22 ♦ Mean age: 7 (20-86) ♦ Prof-D 25.63 T + ◊ General population DM 5.37 T + ◊ Inving in Nachaluay 0: 307 ♦ Based on 32 teeth • Ubonratchathani, Mean age: 547 ◆ Based on 32 teeth •	et al. 2012	Total: 124 ◊	Total	DM type I/II	Missing: 481 ()	Missing: 112 (
With DM: 65 ◆ ♀:57 ⋄ Type of assessment: Patient level: Selected from the Hospital Universitatio Mean age:? Prof-D 20.6 T + ⋄ Hospital Universitatio Ø: 45 ◆ 7.4 T - ⋄ 7.4 T - ⋄ San Vicente de Paul (Medellin, Colombia) Ø: 20 ◆ 7.4 T - ⋄ 7.4 T - ⋄ Non-DM: 59 ⋄ Mean age: 57.4 ⋄ Bassed on 28 teeth ◆ Non-DM: 59 ⋄ Non-DM: 59 ⋄ Bassed on 28 teeth ◆ Non-DM: 59 ⋄ Mean age: 57.4 ⋄ Missing: 2414 ⋄ Valle Mean age: 44.1 ⋄ Missing: 2414 ⋄ Total teeth: 12128 ⋄ Type of assessment: Patient level: Non-DM: 25 ◆ Mean age: 7 (20-86) ◆ Prof-D 25,63 T + ⋄ Wining in Nachaluay Ø: 72 ◆ Prof-D 25,63 T + ⋄ Wonardhaluay Ø: 307 ◆ Bassed on 32 teeth ◆			ರೆ:67 ◊		Total teeth: 1820 ◊	Total teeth: 1652 ◊
Selected from the Hospital Universitario San Vicente de Paul G: 45 ◆ Hospital Universitario San Vicente de Paul G: 45 ◆ Non-DM: 59 ◊ Selected from the School of Dentistry at the Universidad del Ports: 605 ◆ Total: 605 ◆ Non-DM: 226 ◆ Total: 605 ◆ Non-DM: 226 ◆ Non-DM: 226 ◆ Non-DM: 226 ◆ Non-DM: 226 ◆ Nean age: 7 (20-86) ◆ Non-DM: 226 ◆ Non-DM: 226 ◆ Nean age: 7 (20-86) ◆ Non-DM: 226 ◆ Non	ectional	With DM: 65 ♦	♀ : 57 ◊	Type of assessment:		
Selected from the Hospital Universitario DM 20.6 T + ◊ Hospital Universitario DM 7.4 T - ◊ San Vicente de Paul \$\oldsymbol{q}\$: \$45 \\ \$\oldsymbol{q}\$: \$1.20 \\ \$\oldsymbol{q}			Mean age: ?	Prof-D	Patient level:	Patient level:
Hospital Universitario DM San Vicente de Paul O: 45 ◆ (Medellin, Colombia) P: 20 ◆ Non-DM: 59 ◊ Selected from the School of Dentistry at the Universidad del P: 37 ◊ Total: 605 ◆ Non-DM: 379 ◆ DM: 379 ◆ DM: 379 ◆ DM: 379 ◆ O: 22 ◊ Type of assessment: Non-DM: 226 ◆ DM: 379 ◆ O: 22 ◊ Type of assessment: Non-DM: 226 ◆ DM: 379 ◆ O: 25 ◊ Type of assessment: Non-DM: 379 ◆ O: 370 ◆ DM: 370	derate	Selected from the			20.6 T+ ()	26.1T+ ◊
San Vicente de Paul ♂:45 ◆ Based on 28 teeth ◆ (Medellin, Colombia) ♀:20 ◆ Based on 28 teeth ◆ Non-DM: 59 ◊ Non-DM School of Dentistry at School of Dentistry at the Universidad dell ♀:37 ⋄ Wean age: 44.1 ⋄ Missing: 24/4 ⋄ Total: 605 ◆ Total DM type I/II Missing: 24/4 ⋄ DM: 379 ◆ ♀ 475 ⋄ Type of assessment: Prof-D DM: 379 ◆ ♀ 475 ⋄ Prof-D 25,63 T + ⋄ General population DM A:37 + ⋄ 6:37 - ⋄ Ilving in Nachaluay ♂:72 ◆ Aistrict, Based on 32 teeth ◆ Ubonratchathani, Mean age: 547 ◆ Based on 32 teeth ◆		Hospital Universitario	DM		7.4 T- ◊	1.9 T- ◊
Non-DM: 59 ◊ Mean age: 57.4 ◊ Based on 28 teeth • Non-DM: 59 ◊ Non-DM Selected from the School of Dentistry at the Universidad del Q: 37 ◊ Non-DM: 22 ◊ Yalle Mean age: 44.1 ◊ DM type I/II Missing: 2414 ◊ Total: 605 ◆ Total DM type I/II Missing: 2414 ◊ Inving in Nor-DM: 226 ◆ Q* 130 ◊ Type of assessment: Patient level: Non-DM: 226 ◆ Mean age: ? (20-86) ◆ Prof-D 25,63 T + ◊ General population DM 6,37 T - ◊ living in Nachaluay Ø: 307 ◆ Based on 32 teeth ◆ Ubonratchathani, Mean age: 547 ◆ Based on 32 teeth ◆		San Vicente de Paul	♂:45♦			
Non-DM: 59 ◊ Mean age: 57.4 ◊ Mean age: 57.4 ◊ Selected from the School of Dentistry at the Universidad del School of Dentistry at the Universidad del \$\frac{\pi}{\pi}\$: 22 ◊ \frac{\pi}{\pi}\$: 22 ◊ Total: 605 • Total DM type I/II Missing: 2414 ◊ Total: 605 • Total DM type I/II Missing: 2414 ◊ Total: 605 • Total Prof-D Total teeth: 12128 ◊ DM: 379 • \$475 ◊ Prof-D Patient level: 25,63 T + ◊ Non-DM: 226 • DM Prof-D 25,63 T + ◊ General population DM \$4,37 + ◊ \$4,37 + ◊ Iving in Nachaluay \$2,37 + ◊ \$4,37 + ◊ Ubonratchathani, Mean age: 54.7 • Based on 32 teeth •		(Medellin, Colombia)	♀ :20◆		Based on 28 teeth •	Based on 28 teeth ◆
Non-DM: 59 ⟨§ Selected from the School of Dentistry at School of Dentistry at the Universidad del School of Dentistry at the Universidad del \$\phi: 32 \circ\$ \$\phi: 37 \circ\$ Mean age: 44.1 ⟨§ Missing: 2414 ⟨§ \$\phi: 37 \circ\$ Missing: 2414 ⟨§ \$\phi: 37 \circ\$ \$\phi: 37 \cho:			Mean age: 57.4 ≬			
Selected from the School of Dentistry at School of Dentistry at the Universidad del School of Dentistry at the Universidad del 4:12 viscono of Dentistry at the Universidad del 4:13 DM type I/II Missing: 2414 § Total: 605 • Total Total DM type I/II Total teeth: 12128 § DM type I/II Total teeth: 12128 § DM: 379 • Quistrior A 475 § Prof-D Prof-D Patient level: 25,63 T + § Based on 32 teeth • Ubonratchathani, A 537 T - § Based on 32 teeth •		Non-DM: 59 ◊				
School of Dentistry at the Universidad del the Universidad del the Universidad del valle \$\pi\$:37 \(\) \text{Valle} Mean age: 44.1 \(\) \text{Total} DM type I/II Missing: 2414 \(\) Total teeth: 12128 \(\) \text{Total teeth: 12128 \(\) \tex		Selected from the	Non-DM			
the Universidad del		School of Dentistry at	ರೆ:22 ≬			
Valle Mean age: 44.1 ◊ DM type I/II Missing: 2414 ◊ Total: 605 ◆ Total Total teeth: 12128 ◊ Total teeth: 12128 ◊ DM: 379 ◆ ♀ 475 ◊ Type of assessment: Prof-D Prof-D Non-DM: 226 ◆ Mean age: ? (20-86) ◆ Prof-D 25,63 T + ◊ General population living in Nachaluay district, Φ:372 ◆ 6,37 T - ◊ Ubonratchathani, Mean age: 547 ◆ Bassed on 32 teeth ◆		the Universidad del	♀ :37 ◊			
Total: 605 ◆ Total DM type I/II Missing: 2414 ◊ of 130 ◊ Type of assessment: Total teeth: 12128 ◊ DM: 379 ◆ ♀ 475 ◊ Type of assessment: Prof-D Non-DM: 226 ◆ Mean age: ? (20-86) ◆ Prof-D Patient level: General population living in Nachaluay district, Ø: 72 ◆ 6,37 T- ◊ Ubonratchathani, Mean age: 547 ◆ Bassed on 32 teeth ◆		Valle	Mean age: 44.1 (
ع30 ◊ Total teeth: 12128 ◊ DM: 379 • ♀ 475 ◊ Type of assessment: Non-DM: 226 • Mean age: ? (20-86) • Prof-D 25,63 T + ◊ General population living in Nachaluay district, Ubonratchathani, Ubonratchathani, Ø: 377 • Based on 32 teeth •	ırı et al.	Total: 605 ◆	Total	DM type I/II	Missing: 2414 ()	Missing: 694 ()
DM: 379 ◆ \$ 475 ◊ Type of assessment: Prof-D Non-DM: 226 ◆ Mean age: ? (20-86) ◆ Prof-D 25,63 T + ◊ General population living in Nachaluay district, Ubonratchathani, Ubonratchathani, Ø: 37 → Based on 32 teeth ◆			♂ 130 ◊		Total teeth: 12128 ()	Total teeth: 7232≬
Non-DM: 226 ◆ Mean age: ? (20-86) ◆ Prof-D Patient level: 25,63 T + ◊ General population living in Nachaluay district, Ubonratchathani, Ubonratchathani, DM Acist + ◊ Acist + ◊		DM: 379 ◆	9 475 ◊	Type of assessment:		
General population DM 6,37T- ♦ 6,37T- ♦ living in Nachaluay 0:72 ♦ Based on 32 teeth ◆ Ubonratchathani, Meanage: 547 •	ctional	Non-DM: 226 ♦	Mean age: ? (20-86) ♦	Prof-D	Patient level: 25,63 T + ()	Patient level: 28,93 T+ ()
Vachaluay ♂:72 ◆ ♀:307 ◆ Chathani, Mean age: 547 ◆	sno	General population	DM		6,37 T- ◊	3,07 T- ()
\$\delta : 30 \ \phi\$ Chathani, Mean age: 54 7 \phi\$		living in Nachaluay	o³:72♦		◆ \\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	▼ V+~~~+ CC
		uistrict, Ubonratchathani,	♥:30/♦ Mean age: 54.7 ♦		Dased off 52 teetiff ◆	

	Missing: 282184 \(\)	Total teeth: 110908 ◊		Patient level:	Non-DM (compared DMI&II)	19,9 T+ ◊	8,1 T − ◊		Based on 28 teeth ◆		Non-dm (compared DMI)	Missing: 13764 (Total teeth ever: 74116◊		Patient level:	22,8 present teeth (5.2 missing teeth ◆		Non-DM (compared DM II)	Missing: 14454 \(\)	Total teeth: 36792≬		Patient level:	17,0 T+ ◊	11.0 T- •
	Missing: 3414 ()	Total teeth: 9156 ◊		Patient level:	18 T + ◊	10 T- ()		Based on 28 teeth ◆		DM type I	Missing: 885 (Total teeth: 4060≬		Patient level:	21,9 present teeth (6.1 missing teeth ◆		DM type II	Missing: 2530 ◊	Total teeth: 5096≬	•	Patient level:	14,1 T+ ()	13.9 T- +	
	DM type I/II	(data are presented per	type)		Type of assessment:	TIDM Prof-D		SHIP/T2DM: Self-R		Type of assessment:	Self-R (TIDM) and/or	Prof-D (T2DM)													
Non-DM ♂: 58 ♦ ♀: 168 ♦ Mean age: 43.6 ♦	Total	♂ :2055 ◊	♀ :2233 ◊	Mean age: ?		DM	ਹੈ:180 ◊	Q:147 ()	Mean age: 52.5 ≬		Type I	♦ 91: 76 ♦	◊ 69 : 6	Vean age: 37.4 ◆		Type II	o':104◆	\$:78 ()	Mean age; 64.5 ♦	Non-DM	ਹੈ:1875 ◊	♀ :2086 ◊	Mean age: 46.8 ◊		
	Total: 4288 (DM: 327 ◊	DM I: 145 •	DM II: 182 ◆		Non-DM: 3961≬		General population	from the SHIP Trend	study (population-	based survey in North-	Eastern Germany)		TIDM: Centre of	Cardiology and	Diabetes,	Karlsburg							
	VII: Kaur et al. 2009		Oross-sectional	Germany	RoB: Low																				

VIII: Patiño-Marín et	Total: 70 (Total	DM type II	Missing: 200 (Missing: 123 (
al. 2008		ರೆ:33 ◊		Total teeth: 980 (Total teeth: 980 ()
	DM: 35 ◊	♀ : 46 ◊	Type of assessment:		
Cross-sectional		Mean age: ?	Prof-D	Patient level:	Patient level:
Mexico	Non-DM: 35 ◊)		22.3 T+ ◊	24,5 T+ ◊
RoB: Moderate		DM		5.7 T- ◆	3.5 T- ♦
	General population in	ರೆ:14 ◊			
	Mexico.	♀ :21◆		Based on 28 teeth 🔷	Based on 28 teeth ◆
		Mean age: 45 ♦			
		Non-DM			
		0.19 ◊			
		♥ :25 ♦			
IX: Bacic et al. 1989	Total: 411 ()	Total	DM type I/II	Missing: 2731 ()	Missing: 1833 ()
	>	♂ :245 ◊	:: (.)) [()	Total teeth: 7104 (Total teeth: 6048 (
Cross-sectional	DM: 222 ◆	♦ :166 ◊	Type of assessment:		
Croatia	Insulin dependent	Mean age: ?	Prof-D	Patient level:	Patient level:
RoB: Serious	(IDDM)t: 109 ◆			19.7 T+ ()	22.3 T+ ◊
	Non-insulin dependent	DM:		12.3 T-◆	9.7 T-◆
	(NIDDM) 113 •	♂:130◆			
		♀ :92◆		Based on 32 teeth •	Based on 32 teeth ♦
	DM patients: selected	Mean age: 49.6 ◆			
	from the Vk Vrhovac				
	Institute of Diabetes,	Non-DM:			
	Endocrinology and	♂:115◆			
	Metabolic Diseases in	♀ : 74 ◆			
	Zagreb referred from all	Mean age: 43.9 ◆			
	parts of Croatia.				
	Non-DM:189◆				
	Non-DM patients:				
	general population of				
	Croatia during a survey				
	on the prevalence of				
	periodontal disease and				
	carico III Organa.				

X: Falk et al. 1989 Total: 231 ◊		Total	DM type I/II	Missing: 1007 (Missing: 416≬
		ರೆ:112 ◊		Total teeth: 4312 ◊	Total teeth: 2156≬
OM: 154 ◊		♦ :119 ◊	Type of assessment: ?		
ong duratik	ong duration 82 (28.9	Mean age: ?		Patient level:	Patient level:
years)				21,4 T+ ◊	22.6 T+ •
Short durat	Short duration: 72 (5.2	MO		6,6 T- ◊	5.4 T- ◊
years)		ਹੈ:78 ◊			
		\$: 76 ◊		Based on 28 teeth ◆	Based on 28 teeth ◆
Selected from the	om the	Mean age:? (20-70) ◆		:	
Department of	tof			Long duration	
nedicine at	nedicine at the central	Long duration		Missing: 467 ◊	
lospital in 🗸	Hospital in Jönköping,	ರೆ: 40 ♦		Total teeth: 2296 (
Sweden.		♀ : 42 ◆			
				Patient level:	
Non-DM: 77 ◆	* 2	Short duration		22,3 T+ •	
selected from the	ım the	0:38 ◆		5,7 T- ◊	
county council's	cili's	Q · 34 •			
register of persons	ersons	· ·		Short duration	
esiding in th	esiding in the borough	MOJAON		Missing: 540 (
of Jonkoping.	9.	o 34		Total teeth: 2016 (
General population	nolation	Q 43		Patient level:	
		Mean age: ?		20,5T+	
				7,5 T- ()	

Abbreviations: ?, Is not reported/unknown; \(\), Calculated; \(\), Given by the original author; PMT, Periodontal maintenance therapy; PrDM, Previous known diabetes mellitus; Prof D, Professionally diagnosed; RoB, Risk of bias; ScDM, Screening detected diabetes mellitus; Self-R, Self

Assessment of methodological heterogeneity

Eight of the included observational studies utilize a cross-sectional design (I^{42} , IV^{47} , V^{50} , VI^{49} , VII^{44} , $VIII^{48}$, IX^{45} and X^{46}), one is a prospective cohort (II^{43}), and one is a retrospective case-control (III^{40}). Two included papers employ data from national databases: NHANES and KNHANES (I^{42} and IV^{47}), and two papers utilize data from a national study: NFBC-1966, SHIP and HCHS/SOL (VII^{44} and II^{43}). Study III^{40} includes patients who were enrolled in a periodontal maintenance programme. The number of evaluated teeth is 32 in two studies (VI^{49} and IX^{45}) and 28 in eight studies (II^{42} , III^{43} , III^{40} , IV^{47} , V^{50} , $VIII^{44}$ and X^{46}).

Methodological quality assessment

A summary of the methodological quality and potential risk-of-bias scores is presented in Table 3. Detailed quality assessment for each included study is provided in Online Appendix S2. Based on a summary of the bias assessment domains, the estimated potential risk of bias is low for two studies: I^{43} and VII^{44} ; moderate for the majority of the studies: I^{42} , III^{40} , V^{50} , $VIII^{48}$ and V^{46} ; and serious for the remaining three studies: IV^{47} , VI^{49} and IX.

Table 3Summary of the risk of bias assessment using Robins-E tool

For detail see Online Appendix	S2 - 2	S2 - 3	S2-4	S2 - 5	S2-6	S2 - 7	S2-8	82 - 9	S2-10	S2-11
Overall risk of bias	Moderate	Low	Moderate	Serious	Moderate	Serious	Low	Moderate	Serious	Moderate
Bias in selection of the reported result	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	Low
Bias in measureme nt of outcomes	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias due missing data	Low	Low	Low	Moderate	Low	Low	Low	No information	Low	Low
Bias due to departures from intended exposures	Moderate	Low	Low	Serious	Moderate	Moderate	Low	Low	Moderate	Moderate
Bias in classification of exposures	Low	Low	Low	Moderate	Moderate	Serious	Low	Low	Low	Moderate
Bias in selection of participants into the study	Low	Low	Moderate	Low	Moderate	Serious	Low	Moderate	Moderate	Low
Bias due confounding	Moderate	Low	Moderate	Low	Moderate	Low	Low	Moderate	Serious	Moderate
Study	_	=	=	2	>	 >	=		×	×

Study results

From the included studies, the overall DM population consisted of 5.699 patients and the non-DM controls of 23.579 individuals. The overall prevalence of DM in the included cross-sectional studies is 16.8%.

Description of findings

Table 4 describes and summarizes the statistical differences as reported in the original studies between DM patients and non-DM individuals with regard to the number of missing teeth. From the 10 overall comparisons, six provide data and indicate significantly more tooth loss for the DM patients. Four of the included studies do not specify or are unclear whether any statistical differences between the DM and non-DM controls were present.

Table 4A descriptive summary of statistical significance levels of the difference between DM patients compared to non-DM with regard to number of teeth.

Study	Exposure	Number of teeth significance	Comparison
1. Shin et al. 2017	DM	?	non-DM
2. Greenblatt et al. 2016	DM	?	non-DM
3. Costa et al. 2011/2013	DM	+	non-DM
4. Patel et al. 2013	DM	+	non-DM
5. Botero et al. 2012	DM	+	non-DM
6. Sensorn et al. 2012	DM	+	non-DM
7. Kaur et al. 2009	DM	?	non-DM
8. Patiño-Marín et al. 2008	DM	+	non-DM
9. Bacic et al. 1989	DM	+	non-DM
10. Falk et al. 1989	DM	?	non-DM
	0/10 no signific	TAL canty less teeth cant difference t specified	

? unclear/not specified + DM patients have significant less teeth than non-DM

Meta-analysis

The results indicate a higher probability (RR=1.63) of tooth loss for patients with DM as compared to non-DM individuals. This is based on the 10 included studies with a 95% CI (1.33; 2.00, p<0.00001) and shown in Figure 2. The subgroup analysis based on studies that provide data relative to 32 evaluable teeth reveals an RR of 1.51 with a 95% CI (1.45; 1.58, p<0.00001), and for those evaluating 28 potential teeth, the RR was 1.64 with a 95% CI (1.29; 2.08, p<0.0001).

Figure 2.1Meta-analysis evaluating the effect of DM compared to non-DM on tooth loss using a random model: overall and evaluable number of teeth; 28/32 teeth.

	DN	1	no	DM		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.1.1 28 teeth							
Botero et al. 2012	481	1820	112	1652	9.4%	3.90 [3.21, 4.74]	,
Costa et al. 2011/2013	225	1288	183	1288	9.6%	1.23 [1.03, 1.47]	
Falk et al. 1988	1007	4312	416	2156	10.1%	1.21 [1.09, 1.34]	
Greenblatt et al. 2016	10140	78176	20733	181412	10.3%	1.13 [1.11, 1.16]	
Kaur et al. 2009	3414	9156	28218	110908	10.3%	1.47 [1.42, 1.51]	-
Patel et al. 2013	3763	10752	11196	46788	10.3%	1.46 [1.42, 1.51]	-
Patino-Márin et al. 2008	200	980	123	980	9.3%	1.63 [1.32, 2.00]	
Shin et al. 2017	7356	36260	26331		10.3%	2.34 [2.28, 2.39]	•
Subtotal (95% CI)		142744		648592	79.6%	1.64 [1.29, 2.08]	
Total events	26586		87312				
Heterogeneity: $Tau^2 = 0.13$	2; $Chi^2 = 2$	2103.74,	df = 7 (P < 0.000	$(01); I^2 =$	100%	
Test for overall effect: Z =	4.04 (P <	0.0001)					
3.1.2 32 teeth							
Bacic et al. 1989	2731	7104	1833	6048	10.3%	1.27 [1.21, 1.33]	_
Sensorn et al. 2012	2414	12128	694	7232	10.2%	2.07 [1.92, 2.25]	
Subtotal (95% CI)		19232		13280	20.4%	1.62 [0.99, 2.65]	
Total events	5145		2527				
Heterogeneity: $Tau^2 = 0.13$	2; Chi ² = 1	112.39, 0	df = 1 (P)	< 0.0000	1); $I^2 = 9$	9%	
Test for overall effect: $Z =$	1.92 (P =	0.05)					
Total (95% CI)		161976		661872	100.0%	1.63 [1.33, 2.00]	•
Total events	31731		89839				
Heterogeneity: $Tau^2 = 0.1$		2212.78.		P < 0.000	01): I ² =	100%	
Test for overall effect: Z =				51000	/, '		0.5 0.7 1 1.5 2
Test for subgroup difference			,	= 0.97). I ²	= 0%		Favours DM Favours no DM
rest for subgroup different		0.00, u	- 1 (1	- 0.37), 1	- 0/0		

Figure 2.2Meta-analysis evaluating the effect of DM compared to non-DM on tooth loss using a fixed model: overall and evaluable number of teeth; 28/32 teeth.

	DN	1	no	DM		Risk Ratio	Risk Ra	tio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed,	95% CI	
3.1.1 28 teeth									
Botero et al. 2012	481	1820	112	1652	0.4%	3.90 [3.21, 4.74]			•
Costa et al. 2011/2013	225	1288	183	1288	0.6%	1.23 [1.03, 1.47]	-	-	
Falk et al. 1988	1007	4312	416	2156	1.8%	1.21 [1.09, 1.34]			
Greenblatt et al. 2016	10140	78176	20733	181412	41.0%	1.13 [1.11, 1.16]		•	
Kaur et al. 2009	3414	9156	28218	110908	14.1%	1.47 [1.42, 1.51]		-	
Patel et al. 2013	3763	10752	11196	46788	13.8%	1.46 [1.42, 1.51]		-	
Patino-Márin et al. 2008	200	980	123	980	0.4%	1.63 [1.32, 2.00]		•	_
Shin et al. 2017	7356	36260	26331	303408	18.5%	2.34 [2.28, 2.39]			•
Subtotal (95% CI)		142744		648592	90.6%	1.50 [1.48, 1.52]		•	
Total events	26586		87312						
Heterogeneity: $Chi^2 = 210$	3.74, df =	7 (P < 0)	.00001)	$I^2 = 100$	%				
Test for overall effect: Z =	62.63 (P	< 0.0000	1)						
3.1.2 32 teeth									
Bacic et al. 1989	2731	7104	1833	6048	6.5%	1.27 [1.21, 1.33]		-	
Sensorn et al. 2012	2414	12128	694	7232	2.9%	2.07 [1.92, 2.25]			
Subtotal (95% CI)		19232		13280	9.4%	1.51 [1.45, 1.58]		•	
Total events	5145		2527						
Heterogeneity: Chi ² = 112	.39, df = 1	1 (P < 0.0)	00001);	$I^2 = 99\%$					
Test for overall effect: Z =	19.49 (P	< 0.0000	1)						
Total (95% CI)		161976		661872	100.0%	1.50 [1.48, 1.52]		•	
Total events	31731		89839						
Heterogeneity: Chi ² = 221	2.78, df =	9 (P < 0	.00001)	$I^2 = 100$	%		0.5 0.7 1	1,15	
Test for overall effect: Z =							0.5 0.7 1 Favours DM Fa	1.5	2
Test for subgroup differen	ces: Chi ² =	0.25, d	f = 1 (P :	$= 0.62), I^2$	= 0%		Favours DM Fa	Wours no DM	
3 1									

Tables 5 and 6 summarize the detailed data of the outcomes of the meta-analysis and the subgroup analysis including the RR, 95% CI and p-value. Online Appendix S3 presents the corresponding forest plots. Due to a lack of data, it was not possible to perform further sub-analysis on DM details such as insulin dependence and DM duration.

The subgroup analysis on risk of bias for those studies revealed an estimated low risk with an RR of 1.22 and a 95% CI (1.20; 1.24, p<0.00001), an RR of 1.85 with a 95% CI (1.27; 2.71, p=0.001) for those with a moderate risk and an RR of 1.48 at a 95% CI (1.45; 1.52, p<0.00001) for those with a serious risk (for details, see Online Appendix S3.1). When only studies that were originally designed as cross-sectional evaluations were considered, the RR was 1.77 at a 95% CI (1.44; 2.17, p<0.00001; for details, see Online Appendix S3.2).

A subgroup analysis on the world continent in which the study was performed resulted in a RR for Europe of 1.39 at a 95% CI (1.35; 1.42, p<0.0001), North America 1.22 at a 95% CI (1.20; 1.24, p<0.00001), Asia 2.30 at a 95% CI (2.25; 2.36, p<0.00001) and South America 2.27 at a 95% CI (2.00; 2.58, p<0.00001). For all continents, the risk for tooth loss in DM patients was higher as compared to non-DM individuals (for details, see Online Appendix S3.3). Only Study VII⁴⁴ presents usable data for a DM type I group, and therefore, no specific subgroup analysis could be performed. For the studies that solely evaluate DM type II, the RR for tooth loss was 1.56 at a 95% CI (1.02; 2.39, p=0.04; for details, see Online Appendix S3.4). Furthermore, a subgroup analysis on DM status was performed. No significant difference was found regarding tooth loss when well-controlled DM patients were compared to non-DM individuals (RR=1.25 with a 95% CI of 1.22 to 1.29 (p<0.00001)) and also when compared to well-controlled DM patients (RR=1.21 with a 95% CI of 1.17 to 1.26 (p<0.00001)); for details, see Online Appendix S3.5.

Sensitivity analyses were performed by evaluating the effect of excluding studies based on specific aspects in the domain of clinical or methodological characteristics. Sensitivity analysis revealed no differences in the RR compared to the overall RR as judged based on overlapping 95% Cls, indicating that the overall analysis was robust.

Table 5a

Overview (sub) analysis overall and evaluable number of teeth (28/32).

			Effect sizes	sizes		Hetero	Heterogeneity		
Included studies	dies	RR	mode	95 CI%	p-value	l² value	P-value	Funnel plot appendix	For details see
Overall	10 studies	1.63	random	[1.33-2.00]	<0.00001	100%	< 0.00001	S4	Table 5a
Number of teeth	eeth								
32 teeth	Bacic et al. 1989 Sensorn et al. 2012	1.51	fixed	[1.45-1.58]	<0.00001	%66	< 0.00001	84	Table 5a
28 teeth	Botero et al 2012 Costa et al. 2011/2013 Falk et al. 1989 Greenblatt et al. 2016 Kaur et al. 2009 Patel et al. 2013 Patiño-Marín et al. 2008 Shin et al. 2017	1.64	random	[1.29-2.08]	<0.0001	000%	< 0.00001	8S	Table 5a

Table 5b

Overview sub-analysis: risk of bias, study design, world continent, DM type II, DM status

Included studies				Effect sizes		Heter	Heterogeneity	Funnel plot	For details see
		RR	model	%266	p-value	l² value	P value	appendix	
Risk of bias									
Low	Greenblatt et al. 2016 Kaur et al. 2009	1.22	Fixed	[1.20-1.24]	< 0.00001	100%	< 0.00001	S4	53-1
Moderate	Botero et al 2012 Falk et al. 1989 Patiño-Marín et al. 2008 Costa et al. 2013/2011 Shin et al. 2017	1.85	Random	[1.27-2.1]	0.001	%86	< 0.000001	80 40	S3-1
Serious	Patel et al. 2013 Bacic et al. 1989 Sensorn et al. 2012	1.48	Fixed	[1.45-1.52]	< 0.00001	%86	< 0.00001	S4	S3-1
Study design									
Oross sectional	Botero et al 2012 Falk et al. 1989 Kaur et al. 2009 Patel et al. 2013 Patiño-Marín et al. 2008 Shin et al. 2017 Bacic et al. 1989 Sensorn et al. 2012	7.77	Random	[1.44-2.17]	< 0.00001	%66	< 0.000001	84 75	S3-2
World continent									
Europe	Kaur et al. 2009 Bacic et al. 1989 Falk et al. 1989	1.39	fixed	[1.35–1.42]	<0.00001	94%	< 0.00001	S4	S3 - 3
North- America	Greenblatt et al. 2016 Patel et al. 2013 Patific Marin et al. 2008	1.22	fixed	[1.20-1.24]	<0.00001	%66	< 0.00001	84	S3 - 3
Asia South-America	Shin et al. 2017 Sensorn et al. 2012 Costa et al. 2013/2011 Botero et al. 2012	2.30	fixed	[2.25-2.36]	< 0.000001	%68%	0.004	8	S3-3 S3-3

Solely diagnosed as DM type II	as DM type II								
TypeII	Shin et al. 2017	1.56	random	random [1.02-2.39] 0.04	0.04	%001	<0.00001	S4	S3-4
	Costa et al. 2011/2013								
	Kaur et al. 2009								
	Patino-Marin et al. 2008								
Diabetic status									
Well controlled	Greenblatt et al. 2016	1.03	fixed	[1.00-1.06]	0.04	%0	0.88	S4	S3 - 5
vs non-DM	Costa et al. 2011/2013								
Poor controlled	Greenblatt et al. 2016	1.25	fixed	[1.22-1.29	<0.00001	23%	0.25	S4	S3 - 5
vs non-DM	Costa et al. 2011/2013								
Poor vs well	Greenblatt et al. 2016	1.21	fixed	[1.17-1.26]	<0.00001	%0	0.41	S4	S3-5
controlled DM	Costa et al. 2011/2013								

Statistical heterogeneity

Considerable heterogeneity was observed in the meta-analyses; for details see Table 5 and 6. This implies a variation between studies due to heterogeneity rather than chance. To explore heterogeneity, a subgroup analysis was performed to attempt to explain the variation in effects. Subgroup analysis on the evaluated number of teeth, either 28 or 32, revealed an overlap for the 95% CI and with the overall 95% CI. By performing the chi-square test and I², considerable heterogeneity was apparent and varied between 99 and 100%. Subgroup analysis by world continent indicated considerable heterogeneity per continent, ranging from 88 to 99%. Additionally, the meta-analysis of studies solely evaluating DM type II presented considerable (100%) heterogeneity. The three sub-analyses on DM status did not demonstrate important heterogeneity, and the I² statistics were low (0–23%). Subgroup analysis of only studies with an estimated low risk of bias or analyses of studies that were based on an original cross-sectional design illustrate that the I² statistic remains high. It is therefore unclear based on the subgroup and sensitivity analysis what the driver of the high statistical heterogeneity is, although it provides an indication that DM status could be a factor.

Publication bias

Testing for publication bias was possible for the overall analysis, which is presented in Online Appendix S4. The funnel plot reveals that almost all outcomes are located at the top of the funnel, suggesting that no studies concerning small populations were included. Furthermore, the distribution is asymmetrical around the overall value. Consequently, it is presumed that a potential risk for publication bias may exist.

Evidence profile

Table 7 presents a summary of the factors employed to establish the body of evidence profile according to GRADE (2014)²⁰ relative to the magnitude of the risk for tooth loss. In summary, this SR is based on 10 observational studies (Figure 1) and the potential risk of bias was estimated as low to serious (Table 3 and Online Appendix S2). Because data from studies were derived from different populations and world continents, the findings are considered to be generalizable. Based on the heterogeneity between the included studies, data were judged to be rather inconsistent (see Table 2). The data were considered to be rather precise, because all selected studies focused on tooth loss as a primary outcome and because the majority reveal an overlap in the overall 95% CI (see Figure 2, Table 5 and 6 and Online Appendix S3). As publication bias may be present and the funnel plots indicate that outcomes could be overestimated, the presence of reporting bias is likely. The interpretation of the overall RR being 1.63 is that it concerns a small effect.⁵¹ Considering all GRADE aspects, the evidence profile that emerges from this review is that the strength is moderate.

Table 6GRADE evidence profile for the number of teeth and risk ratio among DM as compared to non-DM.

Summary of Findings table on the body of the estimated evidence profile		
Determinants of quality	Risk ratio	
Study design (Table 2)	Observational studies	
#studies (figure 1) #comparisons	# 10 # 10	
Risk of bias (Table 3, Appendix S2)	Low to serious	
Consistency (Table 2)	Rather inconsistent	
Directness	Rather generalizable	
Precision (Figure 2, Table 5 and 6, Appendix S3)	Rather precise	
Reporting bias	Likely	
Magnitude of the effect (Figure 2, Table 5 and 6 Appendix S3)	Small	
Strength of the recommendation based on the quality and body of evidence	Moderate	
Summary and direction of the findings	With respect to tooth loss, there is moderate certainty for a small risk for DM over non-DM.	

DISCUSSION

Untreated dental decay or severe periodontal disease can progress, render a tooth unrestorable or untreatable and lead to extraction as the only option.⁵² The present review summarizes the available body of dental and medical literature with respect to an important question that examines the association between DM and tooth loss. The results of this study indicate a higher probability (RR=1.63) of tooth loss for patients with DM as compared to non-DM individuals. This appears to align with what is reported in other epidemiologic studies, as several have supported the link between DM, periodontal diseases and dental caries.^{53,54} These are the two most common reasons for the endpoint parameter of tooth loss.

Selection choices made

The selection process of the included papers of this SR deviates from the traditional Cochrane approach.¹⁷ However, the foundation is based on similar principles. A two-step approach was utilized: first, screening of titles and abstracts was performed; second, more specific inclusion criteria were implemented to ensure that the only studies included presented data about tooth loss among DM patients and non-DM individuals as the primary outcome. The reviewers are aware that there may be additional information available where data on diabetic status and number of teeth is retrieved from reported demographic data and presented as an interesting result.55-57 Inclusion of these data may introduce a reporting bias that affects the conclusion drawn;58 therefore, it was specifically prespecified that primary outcomes from the study protocol should be included in the final data presentation. The inclusion of reported outcomes should not be based on a selection of results that were not the primary focus of the study.⁵⁹ From a statistical perspective, the sample size of the included studies should have been driven by the primary outcome, which positively affects the power. Consequently, for the present SR, only papers with tooth loss and DM as the primary focus of the original study were sought, and these two aspects had to be mentioned as the aim in the abstract or title. With this approach, it was considered that the most reliable and valid estimation of the RR was obtained.

Diabetes Mellitus comorbidities

For this SR, only DM without reported comorbidities was considered. Papers on participants with other systemic diseases were excluded 60,61 to avoid bias in the observed association between DM and tooth loss. However, DM has many risk factors, such as age, overweight and obesity, inactivity, habitual smoking, food intake, socioeconomic status, family history of DM, geographic region and blood pressure. 62 The included papers did not adjust for these factors. Only in one paper (V50) was smoking specifically mentioned: none of the DM patients reported being smokers, and only non-smoking non-DM individuals were considered as a control group. A range of predictors for tooth loss in periodontitis patients has been reported. A recent SR assesses the consistency and magnitude of different predictors, concluding that age, non-compliance, smoking, DM, teeth with bone loss, high probing pocket depth, mobility and molars, especially with furcation involvement, demonstrate a higher risk of tooth loss. 16 Considering the above, there appears to be an overlap of potential causal components for tooth loss in DM and periodontitis with the following factors: age, smoking habit and DM status. In future studies, it is recommended to include these factors in the analysis. Because the eligible studies of the present review did not report or take these into consideration, the reported outcome allows only for the interpretation of an unadjusted effect size. From the obtained observational data, it is also not possible to make causality claims. As stated earlier, geographical region, sex, type of DM and type wof assessment may interfere in the DM and tooth loss association.

Reporting Bias

The main origin of publication bias is failure to publish negative outcomes or null findings. Additionally, it is more difficult to publish papers in which no differences between groups are found. ^{29,63} The consequences are that this may lead to overestimation of exposure as deducted based on the meta-analyses. ⁶⁴ The present funnel plot (see Online Appendix S4) illustrates that almost all outcomes were located at the top of the funnel, suggesting that relatively few small studies were included. The usage of a strict inclusion criteria may explain this specific distribution. It is recognized that studies with small sample sizes that fail to establish a difference between groups have either not been published or have difficulties in being published in impact factor journals. ⁶³

Type of Diabetes

As prediabetes may be reversible, 65 data from these participants were not considered, as only one study (II43) was available. Gestational DM consists of high blood glucose only during pregnancy 66 and was consequently not analyzed in the present review. Type I DM can develop at any age but occurs most frequently in children and adolescents. However, type II DM, is more common in adults and accounts for approximately 90% of all DM cases. 66 Three of the included studies specifically focus on DM type II (II42, III40 and VIII48). Only one paper (VII44) differentiates between types I and II. It was therefore not possible to perform a subgroup analysis to compare types I and II in this dataset. Analysis focused on DM type II, for which a RR of 1.56 for the risk of tooth loss was found. However, the relationship between DM type II and tooth loss is complicated by the fact that the disease onset generally occurs in middle and late ages, coinciding with the time that periodontitis becomes more prevalent. 44 Nevertheless, studies focusing on type I DM patients also indicate an increased risk of periodontitis compared to non-DM individuals. Study VIII48 includes children, and this group was consequently excluded because children can have temporary, mixed or permanent dentition.

Considerable heterogeneity was observed in the outcomes of most sub-analyses; however, sub-analysis on DM type II did not provide an explanation for the high level of heterogeneity. Only the subgroup analysis on DM status being either poorly or well controlled revealed a low level of statistical heterogeneity (0–23%). This could indicate that DM control is an aspect that contributes to heterogeneity among study outcomes. However, this sub-analysis was based on only two studies that had similar populations and study designs. Because this study's meta-analyses indicated a heterogeneity in the outcome, the reader should exercise caution in utilizing the RR as the exact measure of the risk for tooth loss.

Type of assessment

The Centers for Disease Control and Prevention have estimated that among US individuals, DM is underdiagnosed, which implies that participants in the included studies may have been unaware of their positive DM status. ^{67,68} In that case, it would affect the non-DM group, as these may potentially include DM patients, which thus could result in an underestimation of the effect size. Future research in relation to metabolic status should therefore preferably utilize only those participants who have been clinically diagnosed as DM or non-DM. The majority of the included studies (8 of 10) performed a clinical assessment for DM. Two included studies employed a questionnaire or self-report for DM status. The value of this self-report of disease

in relation to medical records has been demonstrated to have high (>90%) specificity but low sensitivity (66%) for DM 69 .

Evaluable number of teeth

The number of evaluable teeth was assessed by professionally performed oral examinations to obtain optimally reliable values. Two studies that report the number of teeth by utilizing a questionnaire were therefore, in the second phase, excluded.^{70,71} However, both indicate numerically more missing teeth in the DM group as compared to healthy individuals.

Two of the included studies employ data based on 32 evaluable teeth and therefore include wisdom teeth (IX⁴⁵ and VI⁴⁹), while the other eight evaluate 28 teeth. A subgroup analysis was performed with regard to the number of evaluated teeth. There was a numerical difference in RR of tooth loss between those studies evaluating 28 and 32 teeth (1.64 and 1.51, respectively), although the 95% CIs overlap ([95%CI1.29;2.08] and [95%CI1.45;1.58], respectively; see Figure 2 and Table 5a). Therefore, the difference of 0.13 between the RRs does not appear to be significant. Because of this lack of statistical difference for the other sub-analyses, the data from studies with either 28 or 32 evaluable teeth were not separated (see Table 5b as well as Online Appendices S3-1 and S3-5). In the cases in which wisdom teeth are included in the evaluation, prophylactic removal should be considered as a reason for extraction. This aspect was not analyzed in the selected studies that evaluate 32 teeth. The numerically lower but non-significant difference in the analyses of 32 and 28 teeth could be influenced by this. The RR in the sub-analysis with 32 teeth was lower than those studies that evaluate 28 teeth. The lower association with DM could be, in part, the result of prophylactic removal.

Geographical region

From the included cross-sectional studies, the prevalence of DM is 16.8%. The World Health Organization (WHO) published in 2016⁷² the global DM prevalence as 9.2% for adults \geq 18 years. This indicates that the data derived from the included studies are skewed toward DM, which in effect may provide an overestimation of the risk of tooth loss. A recent SR reports the prevalence of DM among subjects with periodontitis by continent. It indicates that the highest prevalence of DM was observed in studies from Asian countries (17.2%) and the lowest for those from Europe (4.3%),23 In the present review, sub-analysis of the risk of tooth loss due to DM by world continent also demonstrates numerical differences. Asia (RR=2.30) had the highest risk, followed by South America (RR=2.27). The 95% CI of the RR of these two continents did not overlap with those of North America (RR=1.22) or Europe (RR=1.39), as both have a lower risk. Apart from comparable differences in the prevalence of DM, the differences in RR per region cannot readily be explained. What could contribute to the findings is that Asians are particularly susceptible to periodontitis73 and that DM is found to be more prevalent compared to other ethnic groups.74,75 The presumed relationship between DM and severity of periodontitis may then be seen as a possible explanation for the relatively high RR. However, no such explanation is available for the higher RR of tooth loss in South America. Study II⁴³ evaluates a specific ethnic group (Hispanics or Latinos) and reports an RR that is lower than the overall RR of the present SR (1.13), which seems to be in line with Arora et al. 76, who compared several ethnic groups in terms of oral health, lifestyle and usage of dental services in the United Kingdom. Individuals belonging to the non-white groups were less likely to report dental extractions and to have fewer than 20 teeth. This may reflect genuinely better oral health. The latter appears to explain the majority of the reduced risk found in Study II.⁴³ However, a study from the USA⁷⁷ suggests that Black individuals are more likely to choose dental extractions. This is mainly explained by preference, treatment acceptability and ability to afford treatment. A recent SR reports no

difference for mean annual tooth loss when comparing geographic groups of North America, Europa, Japan and Oceania versus South America and Asia. Altogether, the above suggests that racial disparities could influence the observed tooth loss, although no clear explanation can be provided for the range in results as observed in the sub-analysis by geographical region.

Sexes

Seven of the included papers feature more females than male participants, while DM type II is more common in males than females. Females generally have a greater knowledge and more positive attitude than males toward oral health behavior. This is associated with a reduced risk for the progression and severity of periodontitis. The skewed sex distribution toward females could cause underestimation of the outcome for this SR.

Risk of bias

Assessment of risk of bias is a key step in conducting SRs and informs many other steps and decisions within the review. It also plays an important role in the final assessment of the strength of the evidence. Sub-analysis based on the overall estimated risk of bias of the selected studies indicates that for low risk of bias, a smaller RR (1.22 and 95%CI[1.20;1.24]) was found than for those with a serious risk (RR=1.48 at a 95%CI[1.45;1.52]). The confidence interval for both low and serious risk of bias was small, which suggests that the estimate is not flawed by imprecision. If the review was restricted to only high methodological quality and low risk of bias studies, then the synthesis of the data concerning the number of teeth in DM patients as compared to non-DM individuals would indicate that the RR for tooth loss is rather small.

Limitations

- The language restriction to English resulted in three potential studies that had to be excluded. Two were in Spanish, 83,84 and one was in Hungarian.85 Based on the information provided in the English abstract, it appears that in these three studies, tooth loss was greater among DM patients as compared to non-DM individuals. These results corroborate the present findings.
- Caries and periodontitis are the predominant reasons for the loss of teeth. None of the included studies considered both aspects as a predictor or confounding factor for tooth loss.
- Factors such as differentiation between DM types I and II, type of assessment (self-report
 or professional), sex and age may have influenced the heterogeneity. This could not be
 further analyzed due to a lack of complete descriptions of the population included in the
 original studies.
- To summarize data from different geographical regions, it was decided to perform subgroup analysis on world continents. The reader should be aware that the reported studies may not capture the true RR of a specific world continent. Some studies have sampled only from small geographic regions, which may not represent the population of the continent.²³

Directions for future research

Despite these limitations, this SR is meaningful and indicates a higher level of tooth loss in DM patients. What is missing is outcomes corrected for aspects such as age and smoking habits. This should be considered in future research.

CONCLUSION

There is moderate certainty evidence for a small but significant higher risk of tooth loss in DM patients as compared to those without DM. Subgroup analysis showed that this was also higher if only DM type II was considered. If the data were separated by the world continent where the study was performed, analysis showed that the magnitude of the risk was particularly higher in Asia and South America.

CLINICAL RELEVANCE

Scientific rationale for the study

DM is a chronic inflammatory disease. Evidence supports an increased risk for periodontal diseases and incidence/severity of caries in DM patients. Both are primary sources of tooth loss. It has not systematically been reviewed whether DM is associated with a higher risk of tooth loss compared to non-DM individuals.

Principal findings

The risk of tooth loss among patients with DM is significantly higher than in non-DM individuals. This risk is higher in Asia and South America than in Europe and North America.

Practical implications

As tooth loss in DM patients was relatively increased oral disease prevention should be the focus of the dental care practitioner in this patient category. In particular, dental care professionals from Asia and South America should be aware that DM may lead to an increased loss of teeth.

Online Appendices



STATEMENTS

Acknowledgements

The authors acknowledge Joost Bouwman, head librarian of the Academic Center for Dentistry Amsterdam, for his help in retrieving the full-text articles. In addition, we thank Jeffrey Knip for his initial work on this topic. The authors also are grateful to the following individuals, who authored papers included in this research, for their responses and for the time and effort they contributed to our search for additional data: T. Similä, M.L. Mayard-Pons, S. Chatrchaiwiwatana, F.O. Costa, H. Luo, H.S. Shin, J. Kapp. N. Dar-Ode, K. Joshipura, J.E. Botero, S.M. Moreno-Correa, F. Teles, T. Tervonen.

Statement of ethics

This study is registered at the International Prospective Register of Systematic Reviews (PROSPERO) by number 140613.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Funding sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. For this study, no funding was accepted, except for support from the listed institution as work for this paper is funded by a regular academic appointment at the Academic Center for Dentistry Amsterdam (ACTA) of Slot and Van der Weijden.

Data statement

More detailed data that support the findings of this study are included in this article and the online appendices. Further enquiries can be directed to the corresponding author.

Author contributions

LPMW: contributed to design, search and selection, analysis and interpretation, and drafted the manuscript.

LZ: contributed to design, analysis and interpretation, and critically revised the manuscript. GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

EWPB: contributed to analysis and interpretation, and critically revised the manuscript. DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

REFERENCES

The papers included in this synthesis are highlighted in **bold** in the list.

- 1. Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NH. Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. *Health Qual Life Outcomes*. 2010;8:126.
- 2. Ramseier CA, Anerud A, Dulac M, Lulic M, Cullinan, Seymour et al. Natural history of periodontitis: disease progression and tooth loss over 40 years. *Journal of clinical periodontology*. 2017;44(12):1182-91.
- 3. Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis et al. Periodontitis and diabetes: a two-way relationship. *Diabetologia*. 2012;55(1):21-31.
- 4. Loë H. Periodontal disease: the sixth complication of diabetes mellitus. Diabetes Care. 1993;16(1):329-34.
- 5. Selwitz RH, Ismail AI, Pitts NB. Dental caries. The Lancet. 2007;369(9555): 51-59.
- 6. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. *The Journal of the American Dental Association*. 2008;139:19S-24S.
- 7. International Diabetes Federation. IDF Diabetes Atlas, 6th edn. (International Diabetes Federation, 2013). Available from: http://www.idf.org/diabetesatlas.
- 8. Linden GJ, Herzberg MC, working group 4 of the joint EFP/AAP workshop Periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AA. *Clinical Periodontology*. 2013;S20-S23.
- 9. Mealey BL, Ocampo GL. Diabetes and periodontal disease. Periodontol. 2000. 2007; 44:127-153.
- 10. Chavarry NG, Vettore MV, Sansone C, Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. *Oral health & preventive dentistry*. 2009;7(2):107-27.
- 11. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with non-diabetics: a meta-analysis. *Journal Diabetes Complications*. 2006;20(1): 59-68.
- 12. Jawed M, Shahid SM, Qader SA, Azhar A. Dental caries in diabetes mellitus: role of salivary flow rate and minerals. *J Diabetes Complications*. 2011;25(3):183-6.
- 13. Mascarenhas P, Fatela B, Barahona I. Effect of diabetes mellitus type 2 on salivary glucose- a systematic review and meta-analysis of observational studies. *PLoS One*. 2014;9(7):e101706.
- 14. American Diabetes Association. Standards of Medical Care in Diabetes-2019. Abridged for primary Care Providers. *Clin Diabetes*. 2019;37(1):11-34.
- 15. Page RC, Eke Pl. Case definitions for use in population based surveillance of periodontitis. *J Periodontol.* 2007;78(75):1387-99.
- 16. Helal O, Göstemeyer G, Krois J, El Sayed KF, Graetz C, Schwendicke F. Predictors for tooth loss in periodontitis patients: Systematic review and meta-analyses. *Journal of clinical periodontology*. 2019;46:699-712.
- 17. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. The Cochrane Collaboration. 2011. Available from: http://handbook-5-1.cochrane.org [Accessed, 20 September, 2019]
- 18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama, Network.* 2000; 283(15):2008-12.
- 19. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ Int. 2018; 121: 1027.
- 20. Morgan RL, Thayer KA, Santesso N, Holloway AC, Blain R, Eftim SE et al. A risk of bias instrument for non-randomized studies of exposures: a users' guide to its application in the context of GRADE. *Environment international*. 2019:122:168-18
- 21. Bero L, Chartres N, Diong J, Fabbri A, Ghersi D, Lam J et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Systematic reviews*. 2018;7(1):242.
- 22. Sterne JAC, Higgins JPT, Elbers RG, Reeves BC. The development group for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance, updated 12 October 2016. Available from http://www.riskofbias.info [Accessed, 20 September, 2019]
- 23. Ziukaite L, Slot DE, Van der Weijden FA. Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies. *Journal of Clinical Periodontology.* 2018;45(6):650-62.
- 24. RevMan: Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*, 2014.
- 25. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Chinese Integr Med.* 2009;7(9):889–96.
- 26. Sambunjak D, Nickerson JW, Poklepovic T, Johnson TM, Imai P, et al. Flossing for the management of periodontal diseases and dental caries in adults. *Cochrane Database of Systematic Reviews*. 2011;(12): 26.
- 27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *Br Med J.* 1997;315:629–34.

- 28. Ryan R. Heterogeneity and subgroup analyses in Cochrane Consumers and Communication Review Group reviews: planning the analysis at protocol stage. [Internet]. Cochrane Consum Commun Rev Group. 2016. Available from: http://cccrg.cochrane.org. [Accessed, 20 September, 2019]
- 29. Van Swaaij BW, Van der Weijden GA., Bakker EW, Graziani F, Slot DE. Does chlorhexidine mouthwash, with an anti-discoloration system, reduce tooth surface discoloration without losing its efficacy? A systematic review and meta-analysis. *International journal of dental hygiene*. 2020;18(1), 27-43.
- 30. Community C. GRADE pro GDT Software [Internet]. Cochrane Community. Available from: http://community.cochrane.org/tools/review-production-tools/gradepro-gdt [Accessed, 20 September, 2019]
- 31. Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: Development and pilot validation. Syst Rev. 2014;3(1):1–9.
- 32. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol*. 2013;66(2):151–7.
- 33. Wiener, RC, Shen C, Findley PA, Sambaoorthi U Tan X. The association between diabetes mellitus, sugar-sweetened beverages, and tooth loss in adults: Evidence from 18 states. *The Journal of the American Dental Association*. 2017;148(7): 500-9.
- 34. Kapp JM, Boren SA, Yun S, LeMaster J. Peer Reviewed: Diabetes and Tooth Loss in a National Sample of Dentate Adults Reporting Annual Dental Visits. Preventing chronic disease. 2007;4(3).
- 35. Jung SH, Ryu JI, Jung DB. Association of total tooth loss with socio-behavioural health indicators in Korean elderly. Journal of oral rehabilitation. 2011;38(7): 517-24.
- 36. Oliver RC, Tervonen T. Periodontitis and tooth loss: comparing diabetics with the general population. *The Journal of the American Dental Association*. 1993;124(12): 71–76.
- 37. Yoo JJ, Kim DW, Kim MY, Kim YT, Yoon JH. The effect of diabetes on tooth loss caused by periodontal disease: A nationwide population-based cohort study in South Korea. *Journal of Periodontology*. 2019;90(6): 576-83.
- 38. Mayard-Pons ML, Rilliard F, Libersa JC, Musset AM, Farge P. Database analysis of a French type 2 diabetic population shows a specific age pattern of tooth extractions and correlates health care utilization. *Journal of Diabetes and its Complications*. 2015; 29(8), 993–97.
- 39. Jimenez M, Hu FB, Marino M, Li Y, Joshipura KJ. Type 2 diabetes mellitus and 20-year incidence of periodontitis and tooth loss. *Diabetes research and clinical practice*. 2011; 98(3): 494-500.
- 40. Costa FO, Miranda Cota LO, Pereira Lages EJ, Soares Dutra Oliveira AM, Dutra Oliveira PA, Cyrino RM, et al. Progression of periodontitis and tooth loss associated with glycemic control in individuals undergoing periodontal maintenance therapy: a 5-year follow-up study. *Journal of periodontology*. 2013;84(5):595-605.
- 41. Costa FO, Miranda Cota LO, Pereira Lages EJ, Vilela Câmara GC, Cortelli SC, Cortelli JR, et al. Oral impact on daily performance, personality traits, and compliance in periodontal maintenance therapy. *Journal of periodontology*. 2011;82(8):1146-54.
- 42. Shin HS. The number of teeth is inversely associated with metabolic syndrome: a Korean nationwide population-based study. *Journal of periodontology*, 2017;88(9):830-38.
- 43. Greenblatt AP, Salazar CR, Northridge ME, Kaplan RC, Taylor GW, Finlayson TL, et al. Association of diabetes with tooth loss in Hispanic/Latino adults: findings from the Hispanic Community Health Study/Study of Latinos. BMJ Open Diabetes Research and Care. 2016;4(1).
- 44. Kaur G, Holtfreter B, Rathmann WG, Schwahn C, Wallaschofski H, Schipf S, et al. Association between type 1 and type 2 diabetes with periodontal disease and tooth loss. *Journal of clinical periodontology*. 2009;36(9):765-74.
- 45. Bačić M, Ciglar I, Granić M, Plančak D, Šutalo J. Dental status in a group of adult diabetic patients. *Community dentistry and oral epidemiology*. 1989;17(6):313-16.
- 46. Falk H, Hugoson A, Thorstensson H. Number of teeth, prevalence of caries and periapical lesions in insulindependent diabetics. *European Journal of Oral Sciences*. 1989;97(3):198-206.
- 47. Patel MH, Kumarc JV, Moss ME. Diabetes and tooth loss: an analysis of data from the National Health and Nutrition Examination Survey, 2003–2004. *The journal of the american dental association*. 2013;144(5):478-85. (
- 48. Patiño Marin N, Loyola RJ, Medina SC, Pontigo, LA, Reyes MJ, Ortega RJ, et al. Caries, periodontal disease and tooth loss in patients with diabetes mellitus types 1 and 2. *Acta Odontol Latinoam.* 2007;21(2):127-33.
- 49. Sensorn W, Chatrchaiwiwatana S, Bumrerraj S. Relationship between diabetes mellitus and tooth loss in adults residing in Ubonratchathani province, Thailand. *J Med Assoc Thai*. 2012;95(12): 1593-605.
- 50. Botero JE, Yepes, FL, Roldán N, Castrillón, CA, Hincapie JP, Ochoa SP, et al. Tooth and periodontal clinical attachment loss are associated with hyperglycemia in patients with diabetes. *Journal of periodontology*. 2012;83(10):1245-50.
- 51. Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. *Communications in Statistics-Theory and Methods*. 2017;46(14):6774–81.
- 52. Elani HW, Harper S, Thomson WM, Espinoza IL, Mejia, GC, Ju X, et al. Social inequalities in tooth loss: a multinational comparison. *Community Dentistry and Oral Epidemiology*. 2016; 45(3):266-74.
- 53. Chapple IL, Genco R, Working group 2 of the joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *Journal of Periodontology.*

- 2013;84:S106-S112.
- 54. Chapple IL, Bouchard P, Cagetti MG, Campus G, Carra MC, Cocco F, et al. Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. *Journal of clinical periodontology*. 2017;44:S39-S51.
- 55. Marotta PS, Fontes TV, Armada L, Lima KC, Rocas IN, Siqueira JF. Type 2 Diabetes Mellitus and the Prevalence of Apical Periodontitis and Endodontic Treatment in an Adult Brazilian Population. *Journal of Endodontics*. 2012;38(3).
- 56. Hopcraft MS, Morgan MV, Satur JG, Clive Wright FA. Edentulism and dental caries in Victorian nursing homes. *The Gerodontology Society and John Wiley & Sons A/S Gerodontology*. 2012;29:512-19.
- 57. Lopez-Lopez J, Jane-Salas E, Estrugo-Devesa A, Velasco-Ortega E, Martin-Gonzalez J, Segura-Egea JJ. Periapical and Endodontic Status of Type II Diabetic Patients in Catalonia, Spain: A Cross-sectional Study. *Journal of Endodontics*. 2011;37(5).
- 58. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *Bmj.* 2010;340.
- 59. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PloS one*. 2008;3(8):e3081.
- 60. Lagervall M, Jansson L. Relationship between tooth loss/probing depth and systemic disorders in periodontal patients. Swedish dental journal. 2007;31;(1):1-9.
- 61. Aoyama N, Suzuki JI, Kobayashi N, Hanatani T, Ashigaki N, Yoshida A, et al. Japanese cardiovascular disease patients with diabetes mellitus suffer increased tooth loss in comparison to those without diabetes mellitus-a cross-sectional study. *Internal Medicine*. 2018;57:(6):777-82.
- 62. International Diabetes Federation. IDF diabetes Atlas Ninth [Internet]. Dunia IDF. 2019. Available from: https://www.diabetesatlas.org/en/. [Accessed, 12 December, 2019]
- 63. Sterne JA, Egger M, Smith GD. Investigating and dealing with publication and other biases in meta-analysis. *Bmj.* 2001; 323(7304):101-5.
- 64. Lundh A, Sismondo S, Busuioc O, Bero L. Industry Sponsorship and Research Outcome. JAMA Intern Med [Internet]. 2013;173(7):580. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2013.4190.
- 65. Tuso P. Prediabetes and lifestyle modification: time to prevent a preventable disease. *The Permanente Journal.* 2014;18(3):88.
- 66. International Diabetes Federation. [Internet]. What is diabetes. Available from: https://idf.org/aboutdiabetes/what-is-diabetes.html. [Accessed, 12 December, 2019]
- 67. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. [Internet]. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011. Available from: www.cdc.gov/diabetes/pubs/pdf/ndfs 2011 pdf. [Accessed, 12 December, 2019]
- 68. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *Journal of Dental Research*. 2012;91:914-920.
- 69. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *Journal of clinical epidemiology*. 2004;57(10):1096-1103.
- 70. Hastings JF, Vasquez E. Diabetes and Tooth Loss among Working-Age African Americans: A National Perspective. Social work in public health. 2017;32(7):443-51.
- 71. Similä T, Auvinen J, Puukka K, Keinänen-Kiukaanniemi S, Virtanen Jl. Impaired glucose metabolism is associated with tooth loss in middle-aged adults: The Northern Finland Birth Cohort Study 1966. Diabetes research and clinical practice. 2018;142:110-19.
- 72. World Health Organization. Diabetes Global Prevalence [Internet]. 2016. Available from: http://www.who.int/mediacentre/factsheets/fs312/en/. [Accessed, 12 December, 2019]
- 73. Corbet EF, Leung WK. Epidemiology of periodontitis in the Asia and Oceanic regions. Periodontol 2000;56:25-64.
- 74. Huxley R, James WP, Barzi F, Patel JV, Lear SA, Suriyawongpaisal P, et al. Obesity in Asia Collaboration. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obes Rev 2008;(1):53–61.
- 75. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301(20):2129-40.
- 76. Arora G, Mackay DF, Conway DI, Pell JP. Ethnic differences in oral health and use of dental services: cross-sectional study using the 2009 Adult Dental Health Survey. *BMC Oral Health*. 2017;17(1):1.
- 77. Tilashalski KR, Gilbert GH, Boykin MJ, Litaker MS. Racial differences in treatment preferences: oral health as an example. *J Eval Clin Pract*. 2007;13(1):102–8.
- 78. Needleman I, Garcia R, Gkranias N, Kirkwood KL, Kocher T, Iorio AD, et al. Mean annual attachment, bone level, and tooth loss: A systematic review. *Journal of clinical periodontology*. 2018;45:S112-S129.
- 79. Diabetes, U. K. Diabetes in the UK 2010: key statistics on diabetes. London: Diabetes UK. [Internet]. 2010. Available

- from: https://www.diabetes.org.uk/resources-s3/2017-11/diabetes_in_the_uk_2010.pdf. [Accessed, 14 December, 2019]
- 80. Liu Y, Yu Y, Nickel JC, Iwasaki LR, Duan P, Simmer-Beck M, et al. Gender differences in the association of periodontitis and type 2 diabetes. *International dental journal*. 2018; 68(6):433-40.
- 81. Baskaradoss JK. Relationship between oral health literacy and oral health status. BMC Oral Health. 2018;18(1):172.
- 82. Viswanathan M, Patnode CD, Berkman ND, Bass EB, Chang S, Hartling L et al. Assessing the risk of bias in systematic reviews of health care interventions. In Methods guide for effectiveness and comparative effectiveness reviews [Internet]. 2017. Agency for Healthcare Research and Quality (US).
- 83. Sampedro CA, Segura JE, Lapetra JP, Llamas RC. Diabetes as a risk factor for tooth loss in the geriatric population. Atencion primaria. 1996;18(4):182-5.
- 84. López-López J, Jané-Salas E, Estrugo-Devesa A, Velasco-Ortega E, Martín-González J, Segura-Egea JJ. Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: a cross-sectional study. Journal of endodontics. 2011;37(5):598-601.
- 85. Albrecht M, Banoczy J, Dinya E, Tamas Jr. G. Caries status in diabetic patients. Fogorvosi szemle. 1991;84(9):267.

"Alles komt goed"

Hein Keijser

CHAPTER NINE

Edentulism among diabetic patients compared to non-diabetic controls

A systematic review and meta-analysis

L. Žiūkaitė*, **L.P.M. Weijdijk*,** J. Tang, D.E. Slot, G.A. van der Weijden *International Journal Dental Hygiene.* 2024;22(1):3-14.

*L.P.M. Weijdijk and L. Žiūkaitė equally contributed to this paper.



ABSTRACT

Objective

The purpose of this paper is to systematically and critically appraise the available scientific evidence concerning the prevalence of edentulism among diabetic (DM) patients compared to non-diabetic people.

Methods

MEDLINE-PubMed and Cochrane-CENTRAL databases were comprehensively searched up to April 2023 to identify appropriate studies. The inclusion criteria were observational studies conducted in human subjects ≥18 years of age with the primary aim of investigating the prevalence of edentulism among DM patients. Based on the extracted data, a meta-analysis was performed. Recommendations based on the body of evidence were formulated using the GRADE approach.

Results

Independent screening of 2085 unique titles and abstracts revealed seven publications that met the eligibility criteria. Study size ranged from 293 to 15,943 participants. Data from all seven studies were suitable for meta-analysis. Overall, 8.3% of the studied population was edentulous. The weighted mean prevalence of edentulism among DM and non-DM was 14.0% and 7.1%, respectively. The overall odds ratio for DM patients to be edentulous as compared to non-DM was 2.39 (95% CI [1.73;3.28], p<0.00001).

Conclusion

There appears to be moderate certainty that the risk of being edentulous for DM patients compared to non-DM people is significant, but the odds ratio is estimated to be small.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic syndrome that results in acute and chronic complications due to the absolute or relative lack of insulin. Evidence exists supporting the association between periodontitis and DM.²⁻⁴ This is a two-way association as has been described by the European Federation of Periodontology manifesto.⁵ Most of the studies that have evaluated DM impact on periodontitis have used surrogate endpoints. In situations where more direct measurements such as tooth retention are not feasible or practical, these indirect outcomes are frequently related to the tooth attachment apparatus. Greenstein has questioned the ability of indirect outcomes to reflect tooth survivability has been questioned because of a lack of long-term data to validate that stable or improved surrogates reduce tooth loss.⁶ True endpoints (e.g., tooth retention or tooth loss) are more meaningful but require long-term and large-scale epidemiological studies.⁷ Tooth loss can be easily assessed and precisely identified by both the patient and the clinician. Furthermore, tooth loss is considered as poor health outcome with a negative impact on a person's quality of life that can lead to difficulty in chewing and speaking, esthetic dissatisfaction, and social stigma.8-12 Investigations using tooth retention as the ultimate endpoint have observed different reasons for tooth extraction, such as orthodontic considerations, prosthetic concerns, caries, and various clinicians' criteria for tooth extraction. The ultimate parameter for tooth loss is edentulism, where the total loss of teeth acts as a surrogate marker for previous serious dental infections and partially reflects antecedent periodontal disease.13 At present, the existing literature on the association between tooth loss and DM has not been synthesized. Therefore, the purpose of this paper is to systematically and critically appraise the available scientific evidence concerning the prevalence of edentulism among DM patients compared to non-DM people.

METHODS

This systematic review's (SR) protocol was developed in the planning stages following discussion between members of the research group. The review was prepared according to the Meta-analysis of Observational Studies in Epidemiology guidelines.¹⁴ This study is registered at the ACTA University Ethical Committee by number 2022-61102.

Focused question

A precise review question was formulated utilizing the population, exposure, comparison, outcomes and study (PECOS)¹⁵ framework as follows:

What is the prevalence of edentulism among DM patients compared to non-DM people established from observational studies?

Search strategy

The authors (LZ, DES) checked all SRs that addressed edentulism for search terms to comprehensively design our search strategy. Three internet sources were used to identify papers that satisfied the study purpose: the National Library of Medicine's PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL). The researchers searched the databases for studies conducted up to April 2023. For details regarding the search terms used, see Table 1. The reference lists of the included studies were hand searched to ensure any additional, potentially relevant studies were included. No further manual searching was performed other than by the Cochrane worldwide handsearching program, which is accessible through CENTRAL. Unpublished work was not sought.

Table 1

Search terms used; the search strategy was customized according to the database being searched. The following strategy was used in the search.

{[<exposure>] AND [<outcome>]}

<Exposure>

("Glucose Metabolism Disorders"[Mesh]) OR ("Diabetes Mellitus"[Mesh]) OR (diabetes mellitus)OR (iddm) OR (niddm) OR (t2dm) OR (t1dm) OR (diabet*)>

AND

<Outcome:>

("Dental Prosthesis" [Mesh]) OR ("Mouth, Edentulous" [Mesh]) OR (dental prosthesis) OR (denture) OR (Jaw, Edentulous) OR (Mouth, Edentulous) OR (loss of teeth) OR (missing teeth) OR (edentul*) OR (toothless) OR (teeth loss) OR (toothloss) OR (tooth loss) OR (tooth loss) OR (tooth loss)

The asterisk (*) was used as a truncation symbol

Screening and selection

Two reviewers (LZ, LW) independently screened the titles and abstracts of eligible papers. If the information relevant to the eligibility criteria was not available in the title or abstract, or if the title was relevant but the abstract was not available, the full text of the paper was read. Complete papers that fulfilled the eligibility criteria were subsequently identified and included in the review.

The eligibility criteria were as follows:

- Human subjects ≥ 18 years of age
- Observational studies (cross-sectional, cohort, or case-control)
- Studies with a primary aim of investigating the prevalence of edentulism among DM patients (specifically mentioned in the title or abstract)
- Studies with the primary aim to investigate DM patients
- Studies of subjects who lived independently (not in nursing homes or other healthcareproviding institutions)
- Studies that consisted of populations reporting to be:
 - People with DM (undefined, type I or type II)
 - People without DM
- Reported outcomes:
 - Prevalence or absolute numbers of subjects wearing complete dentures (in mandibula and maxilla) among DM patients and non-DM people
 - Prevalence or absolute numbers of complete edentulous subjects among DM patients and non-DM people
- Papers written in any language

Any disagreement between the two reviewers was resolved through additional discussion. If a disagreement persisted, the judgement of two other reviewers (DES, GAW) was considered to be decisive. Papers that fulfilled all the selection criteria were processed for data extraction and estimation of the risk of bias. For papers that could not be included in the analysis due to insufficient data, the first or corresponding authors were contacted by e-mail to determine if additional data could be provided.

Assessment of heterogeneity

The heterogeneity across the studies was detailed according to the following factors:

- Study design
- Subjects' characteristics (age, sex)
- Edentulism and DM being self-reported or clinically assessed

Quality assessment

The studies were assessed for potential risk of bias by two reviewers (LW, DES) using the Newcastle-Ottawa Scale (NOS). Disagreement between the reviewers was resolved through discussion and consensus. If disagreement persisted, a third reviewer (GAW) was consulted; this judgement was decisive. In the case of the cross-sectional designed studies, the NOS as described by Herzog et al. Was used; the review authors used a modification of the original NOS items (Online Appendix S1) so that the scale would better address the topic of research. This adaptation of items was previously described by Taggart et al. And used by Hennequin-Hoenderdos et al.

Data extraction

With regard to the focused question, data were extracted from the selected papers by two reviewers (LZ, LW). Disagreement between the reviewers was resolved through discussion and consensus. If disagreement persisted, a third reviewer (DES) was consulted; this judgement was decisive. From the eligible papers, details on study design, demographics and type of DM were extracted. The reviewers' primary interest concerned the prevalence of edentulism

among DM patients compared to non-DM people. If the selected papers did not report the prevalence of edentulism but did report the number of DM patients and non-DM people who were edentulous, the prevalence was calculated by dividing the number of edentulous patients among the DM or non-DM group by the total number of DM patients or non-DM people (for the complete overview, see Table 3).

Descriptive methods

As a summary, a descriptive data presentation was utilised for all studies.

Data analysis

After a preliminary evaluation of the selected papers, the data were first presented in a descriptive manner: the number and percentage of people with edentulism among DM patients and non-DM people were extracted and calculated for each study. A weighted mean prevalence was calculated as a percentage using the SPSS 21.0 statistical package. Studies were assigned weights based on their sample size so that the proportion of information each study contributed to the analysis was considered. It was determined a priori to perform sub-analyses for the assessment method of subjects' DM (self-reported or professionally diagnosed), the assessment method of edentulism (self-reported or clinically assessed) and the origin of the population (by geographical region and by population). A sub-analysis was considered feasible if a minimum of two studies were included. In addition, a meta-analysis was performed using Review Manager software.¹⁹ The odds ratio (OR) was calculated for edentulousness among DM patients compared to those without DM and was interpreted according to Chen et al. 20 less than 1.68 was interpreted as none to very small, 1.68 as small, 3.47 as medium and 6.71 as large. A random- or fixed-effects model was used where appropriate, and a 95% confidence interval (CI) and p-values were also calculated. Heterogeneity was tested using chi-square test and the I² statistic. If significant heterogeneity was found, the random-effects model results were presented. If there were less than four studies, a fixedeffects analysis was performed because if the number of studies is very small it is not always feasible to estimate the between-studies variance (tau-squared) with any precision.²¹ In such a case, the fixed-effects model is the most viable option. The formal testing for publication bias as proposed by Sterne and Egger²² was performed if ≥10 studies could be included in the meta-analysis.²³

Grading the body of evidence

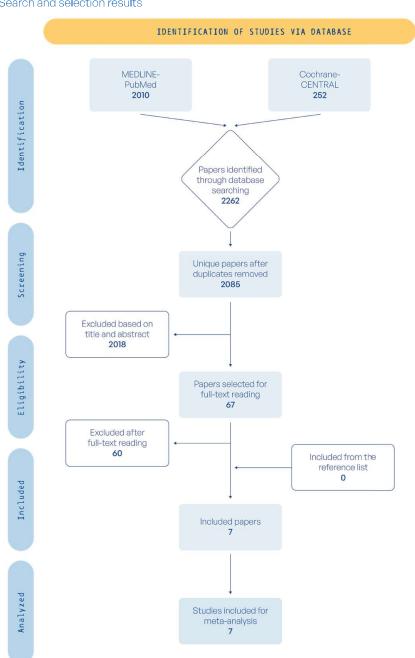
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE), as used by the GRADE working group, ^{24,25} was used to rank the evidence. Two reviewers (DES, GAW) rated the quality of the evidence and the strength and direction of the recommendations according to the following aspects: risk of bias, consistency of results, directness of evidence, precision of data, biases in publication and magnitude of risk. Any disagreement between the reviewers was resolved through additional discussion. If disagreement persisted, a third reviewer (LZ) was consulted; this judgement was decisive.

RESULTS

Search and selection results

The search identified 2085 unique papers (see Figure 1). After screening by titles and abstracts, 67 papers were selected for full-text reading, of which 60 papers were excluded (see Online Appendix S2 for the reasons for exclusion). The reference lists from the selected studies were hand searched, but no additional papers were identified as suitable. Therefore, seven papers²⁶⁻³² were selected and processed for further data extraction. A schematic overview of the search and selection process is presented in the flow chart in Figure 1.

Figure 1
Search and selection results



Assessment of heterogeneity

Extracted data regarding the study designs, characteristics of the study populations, and the diagnostic methods of DM and edentulism are presented in Table 2.

Study design

All included studies used a cross-sectional design. One (I) was part of a prospective cohort study. Four of the included papers evaluated populations in Europe (III, IV, V, VII), two in North America (I, VI) and one study was conducted in South America (II).

Subjects' characteristics

The total number of subjects in each study varied from 293 to 15,943. It is impossible to provide an accurate age range or sex distribution of the studied population as one study (VI) included participants over 50 years of age, another (V) included only men born in 1914 in the city of Malmö in Sweden, and another study from Finland (VII) investigated elderly people living at home. Three papers presented data from national surveys: the National Health and Nutrition Examination Survey in the United States (VI) and the Study of Health in Pomerania in Germany (III: SHIP-Trend, IV: SHIP).

Diagnosis of edentulism and diabetes mellitus

Six included papers assessed edentulism clinically. One study (II) assessed edentulousness based on dental records. Three papers (I, IV, V) presented data where DM was diagnosed professionally and three (II, VI, VII) presented data where DM was self-reported, either through a medical questionnaire (VI) or from dental or medical records (II, VII). The DM in one study (III) was based on both professional assessment and self-reports. In total, three studies specifically focus on DM type II (II, III, VII). One study (VI) did not differentiate between DM type I or II. In three studies DM was not specified (I, IV, V). For the overall calculations, data from these groups were merged. The different types of DM were not further explored. The authors of one of the included studies (III) categorized participants according to their DM status in the following groups: normal glucose tolerance, pre-diabetes, newly detected type 2 DM, known type 2 DM with HbA1c \leq 7.0%, and known type 2 DM with HbA1c \leq 7.0%.

Table 2

Details of included studies

Type of DM	Diagnosis of DM and E
Sexes	Mean age (SD)
(++) (N subjects
	Study design
Included studies	selection ID, authors, year

Included studies selection ID, authors, year country of research	Study design	N subjects Type of population	Sexes Mean age (SD) Range in years	Type of DM Diagnosis of DM and E
I. Greenblatt et al. 2016 ²⁶ United States	Cross-sectional of a prospective cohort study (HCHS/SOL sample)	15943 General population from Hispanic/Latino sample	♂ 6397 ◊ ♀ 9546 ◊ ? (?) 18–74	Type DM: not-specified DM: PD - HbA1c, antidiabetic medications E: CA
II. Islas-Zarazúa et al. 2022 ²⁷ Mexico	Oross-sectional	1921 General population	♂ 684 ♀ 1237 53.91 (10.84) ?	Type of DM: DM2 DM: SR* - DMR (physician diagnosis) E: DMR
III. Kowall et al. 2015 ²⁸ Germany	Cross-sectional survey (SHIP sample)	3623 General population	♂?♀? ?(?) 20 - 82	Type DM: DM2 DM: - SR* (physician's diagnosis + anti-diabetic medication) - PD (WHO 1999) E: CA
IV. Mack et al. 2003?? Germany	Cross-sectional (SHIP sample)	1793 ♦ General population	७११ १ १(१) 55 - 79	Type DM: not specified DM: PD - HbA1c E: CA
V. Norlén et al. 1996³º Sweden	Cross-sectional	483 Male population Men born in 1914 in the city of Malmö in southern Sweden	♂ 483 ♀ 0 68 [68]	Type DM: not specified DM: PD - Blood concentration of glucose E: CA
VI. Patel et al. 2013 ³¹ United States	Cross-sectional of a cohort study (NHANES sample)	2508 General population	ී 121 5 ♀ 1293 ? (?) 50+	Type DMI, DM2 DMI: SR* - Q E: CA
VII. Xie et al. 1999 ³² Finland	Cross-sectional of a survey (HAS sample)	293 General elderly population	♂85 ♀ 208 81≬ [?] [76-86]	Type DM: DM2 DM: SR* - DMR E:CA

?, No data presented or data extraction was not possible; ♂ - male; ♀ - female; ♦ - calculated by the reviewers; data provided by the author: ♦; CA - clinically assessed; DM - diabetes mellitus (DM2: type 2 diabetes mellitus); E - edentulousness; DMR - dental/medical record; PD - professionally diagnosed; Q - questionnaire; SR* - self-reported HCHS/SOL - Hispanic Community Health Study/Study of Latinos, HAS - Helsinki Aging Study

Methodological quality assessment

According to the modified NOS criteria for cross-sectional studies, ¹⁶ five studies (I, II, III V, VI) were considered to have a low risk of bias, two studies (IV, VI) (IV, VII) had a moderate risk, and none had a high risk (Online Appendix S3).

Description of findings

Table 3 describes and summarizes the statistical differences as reported in the original studies between DM patients and non-DM individuals with regard to edentulism. From the 7 overall comparisons, five provide data and two indicate significantly more edentulism for DM patients. Two of the included studies do not specify or are unclear whether any statistical differences between the DM and non-DM controls were.

Table 3A descriptive summary of statistical significance levels of the difference between DM patients compared to non-DM with regard to edentulism.

Study	Exposure	Edentulism significance	Comparison	
I. Greenblatt et al., 2016	DM	?	non-DM	
II. Islas-Zarazúa et al., 2022	DM	+	non-DM	
III. Kowall et al., 2015	DM	?	non-DM	
IV. Mack et al., 2003	DM	0	non-DM	
V. Norlén et al., 1996 DM 0 non-DM			non-DM	
VI. Patel et al., 2013	DM	+	non-DM	
VII. Xie et al.,1999	DM	0	non-DM	
TOTAL				
2/7 have significantly more edentulism 3/7 no significant difference				
2/7 not specified				

Note: ?, unclear/not specified; 0, no difference; +, DM patients have significant more edentulism than non-DM.

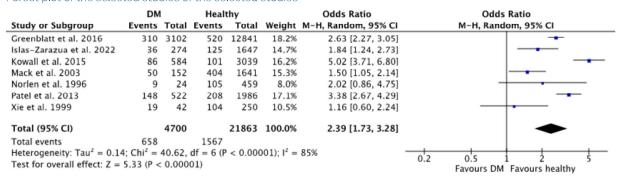
Data analyses

The data extraction revealed that the seven studies involved a total of 2216 edentulous cases. The range of prevalence of edentulism varied from 3.3% to 45% (see Online Appendix S4). The prevalence of edentulism among the whole study population was 8.3%. The overall weighted mean prevalence of edentulism was 14.0% among DM patients and 7.1% among non-DM people. The sub-analysis revealed a prevalence of edentulism of 9.8% and 7.7% for self-reported and clinically assessed DM, respectively. Based on the geographical region, edentulism prevalence was 11.3% for Europe, 6.8% for North America and 8.4% for South America (Table 4). The OR calculated with a random-effects model for DM patients to be edentulous was 2.39 (95% CI [1.73;3.28], based on the data of the seven studies (see Figure 2). ORs were also estimated for self-reported or professionally diagnosed DM and for different geographical regions, which showed a range of 2.39 – 2.61 (Table 5).

Table 4Edentulism prevalence (total population and different sub-groups).

Edentulism prevalence	Edentulism (%)	
Whole studied population	8.3	
o Among subjects without DM	7.1	
o Among subjects with DM	14.0	
Based on the DM assessment		
o Self-report	9.8	
o Professionally diagnosed	7.7	
Based on geographical region		
o Europe	11.3	
o North America	6.8	
o South America	8.4	

Figure 2
Forest plot of the selected studies of the selected studies



A chi-square test resulting in a p<0.1 was considered an indication of significant statistical heterogeneity. As a rough guide for assessing the possible magnitude of inconsistency across studies, an I^2 value of 0–40% was interpreted as non-imperative, and moderate to considerable heterogeneity was assumed to be present for values above 40%

Table 5Odd ratios for DM patients to be edentulous

Analysis	Number of studies included for OR calculation	Model	0	95% CI	OR p-value	Heterogeneity I ²	Heterogeneity p-value
Overall	7	Random	2.39	1.73; 3.28	<0.00001	85%	<0.00001
Sub analysis how DM was measured	neasured						
Self-reported	E	Fixed	2.61	2.15; 3.17	<0.00001	85%	0.001
Professionally diagnosed	c	Fixed	2.39	2.09; 2.73	<0.00001	%9/	0.02
Sub analysis per geographical region	ical region						
Europe	4	Random	2.10	0.95; 4.63	0.07	%16	<0.00001
North-America	2	Fixed	2.82	2.49; 3.20	<0.00001	%89	<0.00001

Grading the body of evidence

Table 6 summarizes the various factors used to rate the quality of evidence and strength of recommendations according to the GRADE working group (2014).²⁴ There was a moderate level of certainty that the magnitude of the OR of being edentulous among a DM population as compared to a non-DM population is small.

Table 6

GRADE evidence profile and the direction of the outcome regarding the prevalence and odds ratio of being edentulous among a diabetic population as compared to a non-diabetic population

Determinants of the quality	Being edentulous	
Study design (Table 2)	Observational studies	
#Studies (Figure 1, Table 2)	#7	
#Comparisons (Figure 1, Table 2, 3)	#7	
Risk of Bias (Online Appendices S1, S3)	Low to Moderate	
Consistency (Table 2, 3, 4, Online Appendix S4)	Rather inconsistent	
Directness (Table 2)	Rather generalizable	
Precision (Table 5, Figure 2)	Precise	
Reporting Bias (text)	Possible	
Magnitude of the odds ratio (Table 5, Figure 2) Small		
Certainty (Table 2, 3, 4, 5)	Moderate	
Overall recommendation	Moderate level of certainty that the magnitude of the OR of being edentulous among a DM population as compared to a non-DM population is small.	

DISCUSSION

Caries and periodontal disease are supposedly more prevalent among DM patients and are the main causes of edentulism. A SR on the prevalence of edentulism among DM patients has not been performed. The present study show that the prevalence of edentulism among DM patients is significantly higher than among non-DM. The loss of teeth is considered the true endpoint for oral diseases; however, the majority of studies concerning the association between DM and oral diseases have instead monitored the number of decayed, missing, and filled teeth. Several indicators of periodontal disease, including pocket depth and clinical attachment loss, have also been studied. Loss of teeth is considered the true endpoint not only from a clinical and anatomical perspective but also from functional and psychosocial viewpoints.³³

A considerable body of literature has covered the link between DM and periodontal diseases.^{2-4, 34,35} The literature also demonstrates that the glucose content of gingival fluid is significantly elevated among DM patients compared to controls,36 which presumably supports the proliferation of microorganisms and enhances their colonization on teeth. Gingival inflammation can influence the protein composition and the prevalence of gingivitis and periodontitis-associated bacteria in the dental biofilm.³⁷ In general, the periodontal condition is of major importance in the rate of de novo plaque formation. In addition, the paper analyzing the relationship between the number of bacteria and plague formation before and after treatment in periodontitis patients suggests that the number of bacteria in the saliva also plays a role.³⁸ The prevalence of dental caries is higher and more severe in DM patients.³⁹ The insulin deficiency in DM may lead to hyposalivation and elevated salivary glucose levels, which may have the consequence that DM patients have a higher risk of caries development.⁴⁰ DM has also been associated with suppression of the killing capacity of neutrophils, which further enhances colonization and thus increases the likelihood of dental caries among DM patients. 41-43 Thus, DM may exacerbate periodontal destruction and dental caries, causing the subsequent loss of affected teeth. 44.45 Consequently, edentulous patients are found to be at higher risk for poor nutrition⁴⁶⁻⁴⁸ which increases the risk of DM.⁴⁹ Furthermore, it has been demonstrated with moderate certainty that DM patients have a slightly higher risk of tooth loss that is nonetheless significant compared to those without DM.50 Therefore, it is important that dental care professionals help to prevent tooth loss with proper dental education, oral health promotion, and a high level of dental care to ensure the existence of physiological well-balanced dentition.⁵¹ This comprehensive review summarizes the available literature to determine the prevalence of edentulism among DM patients compared with non-DM people. It reveals that edentulism is more common in those with diabetes than in those without.

Prevalence of edentulism

The World Health Organization's (WHO) global oral health report⁵² reported the prevalence of edentulism as 26% for adults aged between 65 and 69 from the USA and 41% among adults 65 and over from Finland. The overall prevalence of edentulism in the included studies from the USA was, at 6.8%, markedly lower than that in the WHO's report, while the 42.1% was comparable with the included studies from Finland. A feasible explanation for this difference in the data from the USA is the selection of the study populations. The inclusion criteria of this review consisted of DM patients and non-DM people whereas the WHO collected data from a much broader population. A recent review from Emami et al.⁵¹ reported the prevalence of edentulism in the USA to be 15% in those between 65 and 75 years old and 22% in those over 75. The comparable prevalence to the included Finnish papers can be explained by the higher age of the included participants. Another consideration when comparing the different

prevalences found in literature is that only two studies from the current review were conducted before 2003. This could imply that the general prevalence of edentulism has decreased in recent years.⁵³ This can be attributed to increased awareness in patients regarding personal oral care, improved focus on prevention in dentistry as a whole, the improved financial situation of patients, or a decrease in invasive dentistry.^{54,55}

Diabetes diagnosis and control

The authors of one of the included studies (III) categorized participants according to their DM status in the following groups: normal glucose tolerance, pre-diabetes, newly detected type 2 DM, known type 2 DM with HbA1c < 7.0%, and known type 2 DM with HbA1c \ge 7.0%. They found that there was no consistent association between pre-diabetes and edentulism. Furthermore, the authors suggested that it is important to differentiate between poorly and well-controlled DM: they found no increased prevalence of edentulism in well-controlled DM but did find an association between edentulism and poorly controlled DM. Sub-group analysis was performed according to the DM assessment method (self-reported or professionally diagnosed). When the papers were organized in this way, the prevalence of edentulism appeared to be higher for patients with self-reported as opposed to clinically assessed DM (Table 4). However, the selected papers for this review did not provide sufficient information to explain this difference.

Strength and limitations

The strength of this review paper is that four of the included studies (I, III, IV, VI) analyzed population-based data: this amounts to 96% of the total studied populations included in the studies selected for this review. One can, therefore, consider the outcome of this review to be fairly generalizable. Most of the studies specifically described the overall systemic health of the patients apart from their DM status. Study I collected and reported data regarding the number of diseases but did not specify them. A paper from Sweden (V) investigated how males perceived their general health. Another paper (VII) reported data on heart failure and hypertension. However, it is likely that DM patients and non-DM also suffered from other systemic diseases that were unreported or undiagnosed. From a broader perspective, a limitation of this review is that all the included studies were cross-sectional, which prohibits any inference of causative relationships. However, the findings are clearly consistent with the observation that DM patients have a higher likelihood of edentulism than non-DM people. When interpretating the results of this study, the prevalence of general edentulism should be considered as tooth loss is often a condition resulting from the dentist's decision. When comparing countries the oral care system may differ and can influence the judgement, this aspect is not considered. For future research it is of interest to evaluated what the influence of the oral care system is on edentulism. To ensure the highest level of accuracy possible, only studies that specifically investigated the prevalence of edentulism among DM patients were included in this review. Despite these limitations, this SR is meaningful and indicates a higher prevalence of edentulism in DM patients. However, outcomes on DM differentiation such as type and regulation and smoking habits shall be considered in future research and as important reporting aspect for publications.

Publication bias

Researchers have considered selective outcome reporting to be a major problem deserving of substantially more attention than it currently receives.⁵⁶ Selective reporting of primary outcomes can include choosing which outcomes are reported (discrepancy in identity), how the outcome is defined (discrepancy in definition), and what amount of information is reported for an outcome (completeness of reporting).⁵⁷ To minimize the publication bias related to selective outcomes, the authors specifically decided to only include studies that primarily aimed to investigate the association between edentulism and DM from general populations; that is, the research group made a methodological choice to exclude papers that chose to evaluate an edentulous or diabetic population exclusively.

Cautious interpretation

One of the primary difficulties in studying links between periodontitis and systemic disease is the overlapping risk factors for many systemic diseases and periodontitis, such as age, sex, smoking, obesity, socio-economic status, and so forth. This is known as confounding, and when dental professionals describe links between periodontitis and systemic disease to patients one should bear in mind that possible confounding factors can contribute to periodontal disease and are, therefore, not the only reason for a particular condition. While useful evidence for the association between periodontitis and various systemic diseases (particularly atherosclerotic cardiovascular disease and DM) now exists, causative evidence is still lacking. Researchers acknowledged that the gaps in our knowledge remain large.⁵⁸ Treating periodontal disease while addressing other modifiable risk factors such as smoking, DM control, and diet can also have a positive effect on related systemic diseases. Dental professionals, as frontline health staff, are ideally situated for promoting patients' oral health and benefiting their general health. A green paper⁵⁹ by the European Federation of Periodontology that calls for global action suggests that periodontitis, as one the main cause of edentulism, shares risk factors with other non-communicable diseases such as heart disease and DM. The common risk factor approach, strongly advocated by the WHO for improving human health, should incorporate self-performed oral hygiene as integral part of a healthy lifestyle. Preventive programs for non-communicable diseases should thus consider the specific needs to effectively support oral health as one of the fundamental components of general health60 and include them in large-scale population efforts whenever feasible. Notably, the FDI World Dental Federation's new definition of oral health recognizes its multidimensional nature and attributes (i.e., disease status, physiological function, and psychosocial function) and promotes the incorporation of oral health into mainstream healthcare for effective advocacy of optimal oral and general health. 61,62 Overall, the literature also suggests that aspects of lifestyle might be related to the variations in the prevalence of edentulism.

CONCLUSION

Within the limitations of this review there appears to be moderate certainty that the risk of being edentulous for DM patients compared to non-DM people is significant, but the odds ratio is estimated to be small.

CLINICAL RELEVANCE

Scientific rationale for the study

One of the main causes of edentulism, caries and periodontal disease, are supposedly more prevalent among DM patients. So far, a comprehensive assessment about the prevalence of edentulism among DM patients has not been performed.

Principal findings

The prevalence of edentulism among DM patients is significantly higher than among non-DM people.

Practical implications

Tooth loss may occur because of various factors such as periodontitis or caries both of which are a sequel associated with DM. As the present review has established that DM status is significantly related to edentulism, DM patients should be cognizant that they are at a slightly higher risk of tooth loss.

Online Appendices



STATEMENTS

Acknowledgements

The authors acknowledge the support of Joost Bouwman, head librarian of the Academic Centre for Dentistry Amsterdam, who helped in the retrieval of the full-text articles. The authors are also grateful to the following investigators for their response, time, and effort in searching for additional data, thus contributing to the completion of this systematic review: S. Ajwani, T. Dietrich, P.M. Duarte, S. Elangovan, B. Holtfreter, M.S. Hopcraft, R. Jacobs, S.J. Janket, Y. Jiang, T. Kocher, B. Kowall, J.H. Lee, and C.E. Medina-Solis.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Funding information

Work for this paper was funded by regular academic appointments at the Academic Centre for Dentistry Amsterdam (ACTA) and in part sponsored by an unrestricted grant to Van der Weijden by Procter & Gamble Global Oral Care Professional and Clinical Operations.

Data availability

The data that supports the findings of this study are included in this article and the onlince appendices.

Author contributions

- L. Ziukaite: contributed to search and selection, analysis and interpretation, and critically drafted the manuscript.
- L. Weijdijk: contributed to the design, search and selection, quality assessment, analysis and interpretation of data, and critically revised the manuscript.
- J. Tang: contributed to the design, analysis and interpretation of data and helped draft the manuscript.
- D.E. Slot: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.
- G.A. Van der Weijden: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

REFERENCES

The papers included in this synthesis are highlighted in **bold** in the list.

- 1. Ship JA. Diabetes and oral health: an overview. J Am Dent Asso 2003;134:4S-10S.
- 2. Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: Systematic review of epidemiologic observational evidence. J Clin Periodontol 2013;40:S135-S152.
- 3. Chávarry NGM, Vettore MV, Sansone C, Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. Oral Health & Prev Dent 2009;7:107–127.
- 4. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. JDC 2006;20:59–68.
- 5. European Federation of Peridontology. (2012). EFP Manifesto: Perio and General Health. . Available from: https://www.efp.org/fileadmin/uploads/efp/Documents/Manifesto/EFP_manifesto_ful l_version_2018.pdf [Accessed May 12, 2022].
- 6. Greenstein G. The use of surrogate variables to reflect long-term tooth survivability. J periodontol 2005;76:1398–1402.
- 7. Fleming TR. Evaluating Therapeutic Interventions: Some Issues and Experiences. Stat Science 1992;7:428-456.
- 8. Beltrán-Aguilar ED, Barker LK, Canto MT, Dye BA, Gooch BF, Griffin SO, Hyman J, Jaramillo F, Kingman A, Nowjack-Raymer R, Selwitz RH, Wu T, Centers for Disease Control and Prevention (CDC). Surveillance for dental caries, dental sealants, tooth retention, edentulism, and enamel fluorosis—United States, 1988-1994 and 1999-2002. Morbidity and Mortality Weekly Report. Surveillance Summaries (Washington, D.C.: 2002) 2005;54:1–43.
- 9. Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NHJ. Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. Health Qual Life Outcomes 2010;8:126.
- 10. Sheiham A, Cushing AM, Maizels JE. The social impact of dental disease. In: Slade GD ed. Measuring Oral Health and Quality of Life. Chapel Hill, N.C.: Department of Dental Ecology, School of Dentistry, University of North Carolina, 1997:47–56.
- 11. Starr J M, Hall R. Predictors and correlates of edentulism in healthy older people. Curr Opinion in Clin Nutrition Metabolic Care 2010;13:19–23.
- 12. U.S. Department of Health and Human Services. Oral Health in America: A Report of the Surgeon General National Institute of Dental and Craniofacial Research (2000). Available from: http://www.nidcr.nih.gov/DataStatistics/SurgeonGeneral/Report/ExecutiveSummary.htm [Accessed May 12, 2022]
- 13. Joshipura K, Ritchie C, Douglass C. Strength of evidence linking oral conditions and systemic disease. Compend Contin Educ Dent 2000:30:12–23.
- 14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. J Am Med Assoc 2000;283:2008–2012.
- 15. R.L. Morgan, P. Whaley, K.A. Thayer, H.J. Schünemann. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ. Int., 121 (1) (2018), pp. 1027-1031.
- Herzog R, Alvarez-Pasquin MJ, Diaz C, Del Barrio JL, Estrada JM, Gil A. Newcastle-Ottawa Scale adapted for cross-sectional studies. 2013;available from: http://www.biomedcentral.com/content/supplementary/1471-2458-13-154-S3.doc [Accessed May 12, 2022]
- 17. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet 2001;358:870–875.
- 18. Hennequin-Hoenderdos NL, Slot DE, Van der Weijden GA. The incidence of complications associated with lip and/or tongue piercings: a systematic review. Int J Dent Hyg 2016;14:62–73.
- 19. Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen:
- 20. The Nordic Cochrane Centre, The Cochrane Collaboration, 2011
- 21. Chen H, Cohen P, Chen S. How big is a big odds ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. Commun Stat Simul Comput. 2010;39(4):860-864. doi:10.1080/03610911003650383
- 22. Borenstein M, Hedges LV, Higgins J, Rothstein HR. A basic introduction to fixed effect and random effects models for meta analysis. Res Synth Methods 2010;1:97–111.
- 23. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001;54:1046–1055.
- 24. Higgins JPT, Green S. CCHB Cochrane Handbook for Systematic Reviews of Interventions. 2009;available from: http://handbook.cochrane.org/ [Accessed May 12, 2022].
- 25. N. Meader, K. King, A. Llewellyn, G. Norman, J. Brown, M. Rodgers, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. Syst. Rev., 3 (2014), p. 82.
- 26. G. Guyatt, A.D. Oxman, S. Sultan, J. Brozek, P. Glasziou, P. Alonso-Coello, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J. Clin. Epidemiol., 66 (2) (2013), pp. 151-157.

- Greenblatt AP, Salazar CR, Northridge ME, Kaplan RC, Taylor GW, Finlayson TL, Qi Q, Badner V. Association of diabetes with tooth loss in Hispanic/Latino adults: findings from the Hispanic Community Health Study/Study of Latinos. BMJ 2004;4 e000211.
- 28. Islas-Zarazúa R, Mora-Acosta M, Navarrete-Hernández JJ, Reynoso-Vázquez J, Villalobos-Rodelo JJ, Rojas-Ortega L, Sosa-Velazco TA, Márquez-Corona ML, Medina-Solís CE, Maupomé G. Comparative Analysis of Edentulism in a Sample of Mexican Adults with and without Type 2 Diabetes. Healthcare (Basel). 2022 Nov 26;10(12):2378. doi: 10.3390/healthcare10122378. PMID: 36553901; PMCID: PMC9777753.
- Kowall B, Holtfreter B, Völzke H, Schipf S, Mundt T, Rathmann W, Kocher T. Pre-diabetes and well-controlled diabetes are not associated with periodontal disease: The SHIP Trend Study. J Clin Periodontol 2015;42:422– 430.
- 30. Mack F, Mundt T, Mojon P, Budtz-Jørgensen E, Schwahn C, Bernhardt O, Gesch D, John U, Kocher T, Biffar R. Study of Health in Pomerania (SHIP): Relationship among socioeconomic and general health factors and dental status among elderly adults in Pomerania. Quintessence Int 2003;34(10):772-8.
- 31. Norlén P, Johansson I, Birkhed D. Impact of medical and life-style factors on number of teeth in 68-year-old men in southern Sweden. Acta Odontol Scand 1996;54(1):66-74.
- 32. Patel M H, Kumar J V, Moss M E. Diabetes and Tooth Loss: An analysis of data from the National Health and Nutrition Examination Survey, 2003–2004. J Am Dent Assoc 2013;144:478–485.
- 33. Xie Q, Ainamo A. Association of edentulousness with systemic factors in elderly people living at home. Community Dent Oral Epidemiol 1999;27:202–9.
- 34. Elias AC, Sheiham A. The relationship between satisfaction with mouth and number and position of teeth. J Oral Rehabil.1998;25:649–661.
- 35. Bullon P, Newman HN, Battino M. Obesity, diabetes mellitus, atherosclerosis and chronic periodontitis: a shared pathology via oxidative stress and mitochondrial dysfunction? Periodontol 2000 2014;64:139–153.
- 36. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, Stevenson B, Furness S, Iheozor-Ejiofor Z. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. CDSR 2015;11:CD004714.
- 37. Ficara AJ, Levin MP, Grower MF, Kramer GD. A comparison of the glucose and protein content of gingival fluid from diabetics and nondiabetics. J Periodontal Res 1975;10:171–175.
- 38. Rüdiger SG, Carlen A, Meurman JH, Kari K, Olsson J. Dental biofilms at healthy and inflamed gingival margins. J Clin Periodontol 2002;29:524–530
- 39. Dahan M, Timmerman MF, Van Winkelhoff AJ, Van der Velden U. The effect of periodontal treatment on the salivary bacterial load and early plaque formation. J Clin Periodontol 2004;31(11):972-7.
- 40. Coelho AS, Amaro IF, Caramelo F, Paula A, Marto CM, Ferreira MM, Botelho MF, Carrilho EV. Dental caries, diabetes mellitus, metabolic control and diabetes duration: A systematic review and meta-analysis. J Esthet Restor Dent. 2020 Apr;32(3):291-309.
- 41. Jurysta C, Bulur N, Oguzhan B, Satman I, Yilmaz TM, Malaisse WJ, Sener A. Salivary glucose concentration and excretion in normal and diabetic subjects. J Biomed Biotechnol. 2009;2009;430426.
- 42. Borg Andersson A, Birkhed D, Berntorp K, Lindgärde F, Matsson L. Glucose concentration in parotid saliva after glucose/food intake in individuals with glucose intolerance and diabetes mellitus. Eur J Oral Sci 1998;106:931–937.
- 43. Insuela D, Coutinho D, Martins M, Ferrero M, Carvalho V. Neutrophil Function Impairment Is a Host Susceptibility Factor to Bacterial Infection in Diabetes', in O. Fuchs, S. S. Athari (eds.). Cells of the Immune System, IntechOpen, London:10.5772/intechopen.86600.
- 44. Singh A, Thomas S, Dagli R J, Kat R, Solanki J, Bhateja GA. To access the effects of salivary factors on dental caries among diabetic patients and non diabetic patients in Jodhpur City. J Advanced Oral Res 2014; 5:10–14.
- 45. Aida J, Ando Y, Akhter R, Aoyama H, Masui M, Morita M. Reasons for permanent tooth extractions in Japan. J Epidemiol/Japan Epidemiol Ass 2006;16:214–249.
- 46. Chestnutt IG, Binnie VI, Taylor MM. Reasons for tooth extraction in Scotland. J Dent 2000;28:295–297.
- 47. Felton, DA. Edentulism and comorbid factors. Journal of Prosthodont 2019;18:88–96.
- 48. Naka O, Anastassiadou V, Pissiotis A. Association between functional tooth units and chewing ability in older adults: a systematic review. Gerodontol 2014;31:166–177.
- 49. Ritchie CS, Joshipura K, Hung HC, Douglass C W. Nutrition as a mediator in the relation between oral and systemic disease: associations between specific measures of adult oral health and nutrition outcomes. Critical Reviews in Oral Biology and Medicine: An Official Publication of the American Association of Oral Biologists 2002;13:291–300.
- 50. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nut 2004;80:348–356.
- 51. Weijdijk LPM, Ziukaite L, Van der Weijden GAW, Bakker EWP, Slot DE. The risk of tooth loss in patients with diabetes: A systematic review and meta-analysis. Int J Dent Hyg 2022;20(1):145-166.
- 52. Emami E, de Souza RF, Kabawat M, Feine JS. The impact of edentulism on oral and general health. Int J Dent. 2013;2013:498305
- 53. Petersen PE. The World Oral Health Report 2003: continuous improvement of oral health in the 21st century the approach of the WHO Global Oral Health Programme. Community Dent Oral Epidemiol 2003;31:3–24.
- 54. Müller F, Naharro M, Carlsson GE. What are the prevalence and incidence of tooth loss in the adult and elderly

- population in Eruope? Clin Oral Implants Res 2007;18:2-14.
- 55. Jingarwar MM, Bajwa NK, Pathak A. Minimal intervention dentistry a new frontier in clinical dentistry. JCDR 2014;8:ZE04–ZE08.
- 56. Patel R (2012). The state of oral health in Europe. Report Commissioned by the Platform for Better Oral Health in Europe. Available from: http://www.oralhealthplatform.eu/wp-content/uploads/2015/09/A5-Summary-BOHEP_State-of-Oral-Health_Executive-Summary_A5_FINAL.pdf [Accessed May 12, 2022]
- 57. Tannock IF. False-Positive Results in Clinical Trials: Multiple Significance Tests and the Problem of Unreported Comparisons. J Natl Cancer Instit 1996;88(3/4): 206–207.
- 58. Ghersi D. Issues in the design, conduct and reporting of clinical trials that impact on the quality of decision making. https://ses.library.usyd.edu.au/handle/2123/6653# [Accessed May 12, 2022]
- 59. Linden GJ, Hersberg MC, working group 4 of the joint EFP/AAP workshop. Periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol 2013;84:S20-23.
- 60. Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: A call for global action. J Clin Periodontol. 2017 May;44(5):456-462.
- 61. United Nations General Assembly. (2011). Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases (16 September 2011) (accessed September 20, 2023).
- 62. Glick M, Williams DM, Kleinman DV, Vujicic M, Watt RG, Weyant RJ. A new definition for oral health developed by the FDI World Dental Federation opens the door to a universal definition of oral health. Int Dent J 2016;66:322–324.
- 63. Lee JY, Watt RG, Williams DM, Giannobile WV. A new definition for oral health: Implications for clinical practice, policy, and research. J Dent Res 2017;96:125–127

"Ik heb d'r nich veur keuzn Tukker te wean, ik heb gewoon onmeunig mazzel had"

mama, papa & Wessel

CHAPTER TEN

General summary, discussion and conclusion



The relationship between systemic health and oral health has extensively been discussed over the past decades. For instance, numerous studies have found an association between diabetes mellitus (DM) and oral diseases, indicating a higher risk of periodontitis and caries. ¹⁻³ Although a considerable amount of supporting evidence exists, it is important to address the actual nuances and complexities of this relationship. Moreover, providing accurate insights into the strength of this so called 'systemic link' is important. The research presented in this thesis aimed to explore how DM and some aspects of oral health are interrelated and to offer practical recommendations for the daily clinical practice for dental care professionals.

Bidirectional relationship

With growing evidence suggesting a bidirectional association between systemic health and oral health, there is a need for thorough evaluation. According to the Merriam-Webster dictionary, the term 'bidirectional' is defined as involving, moving, or occurring in two usually opposite directions.4 Research predominantly focuses on the impact of oral health on systemic diseases. Dental researchers, in particular, tend to emphasize the connection between oral and systemic health. In contrast, the reciprocal relationship - the influence of systemic conditions on oral health - receives comparatively less scientific attention. There remains a notable gap in knowledge and awareness of the bidirectional link among medical care workers such as physicians and specialists.^{5,6} A bibliometric analysis conducted in 2022 on the relationship between DM and oral health found that the top 12 journals publishing the most articles on this subject were all dental-focused journals. Additionally, the three journals with the highest number of related publications were those specializing in periodontal diseases.⁷ Another study examining research on DM associated periodontal disease revealed that Dentistry, Oral Surgery & Medicine was the primary field of study, with nearly seven times as many publications as in General & Internal Medicine. This shows the limited attention given to this topic by the broader medical community. Among individuals with DM oral diseases, particularly periodontitis, have become health concerns.

Interpretation strength and effect sizes

Evaluating proportions in a scientific manner is traditionally performed by the use of statistical tests. Interpreting these test results is essential to gain a more accurate understanding of the data and its clinical relevance, providing valuable guidance for dental care professionals. Therefore, when interpreting the results as presented in this thesis, not only the statistical significance should be considered but also the effect sizes. This provides a more realistic understanding of the practical and clinical relevance of the findings. To support the interpretation of these findings, Table 1 presents a detailed overview of significance levels and meta-analysis outcomes, including relative risk (RR), odds ratio (OR), hazard ratio (HR), standardized mean difference (SMD), clinical attachment level differences (CAL), and tests for heterogeneity (I²), along with guidelines for their interpretation in the context of clinical relevance.

Table 1Interpretation of statistical measures in clinical context

Significance(p) ¹²	Not significant outcomes: p≥0.05 Significant outcomes: p<0.05			
Meta-analysis outcome	None	Small	Medium	Large
(RR) ¹³	RR 0	RR>1.22	RR >1.86	RR >3.00
Meta-analysis outcome	None	Small	Medium	Large
(OR) ¹⁴	OR 0	OR>1.68	OR>3.47	OR>6.71
Meta-analysis outcome	None	Small	Medium	Large
(HR) ¹⁵	HR 0	HR>1.68	HR>3.43	HR>6.52
Meta-analysis outcome	None	Small	Medium	Large
SMD ¹⁶	SMD 0	SMD>0.2	SMD>0.5	SMD>0.8
Meta-analysis outcome	Zero	Small	Moderate	Substantial
CAL ¹⁷	CAL 0.2	CAL>0.2	CAL>0.4	CAL>0.6
Test of heterogeneity (I ²) ¹²	Potential not important 0–40%	Moderate 30-60%	Substantial 50–90%	Considerable 75–100%

abbreviations: RR: risk ratio; OR: odds ratio; HR: hazard ratio; SMD: standardized mean difference; CAL: clinical attachment level.

While statistical significance indicates whether an effect is likely not due to chance, it does not convey the magnitude or importance of that effect or strength. Effect sizes, on the other hand, are a measure of the strength of the relationship between variables and help contextualize clinical relevance. A small p-value can reflect a statistically significant result, but if the effect size or strength is negligible to small, the actual magnitude or change may be insignificant in clinical practice. Conversely, even when statistical significance is not achieved, a large effect size or strength may indicate a meaningful association that warrants further investigation. Therefore, in evaluating study results, emphasis should be placed on the practical implications of the effect sizes and strengths, as they provide more insight into the true impact of DM on the oral condition.

In epidemiological research, the Bradford Hill criteria provide a valuable framework for evaluating whether an observed association between an environmental factor and a disease is likely to reflect a causal relationship. It offers a basis to evaluate the strength of the evidence supporting a causal relationship²⁰ and go beyond statistical significance, focusing on the quality and strength of the association. The list of criteria (see Table 2) includes the strength of association, consistency, coherence, specificity, temporality, dose–response relationship, biological plausibility, (quasi) experimental evidence, and analogy.²⁰

Studies frequently report significant associations or correlations without clear biological explanations or a meaningful translation into clinical relevance, especially within systemic and oral health research. This practice often leads to claims of association without sufficient interpretation of the clinical impact, making it challenging for the dental care professional to assess true relevance for patient care.

Table 2Interpretation of the Bradford Hill criteria

Criteria	Meaning
Strength of association	A strong association is more likely to have a causal component than is a modest association. Strength of the association is determined by the types of existing studies. The highest-level studies from the evidence pyramid would represent the strongest associations (i.e., RCTs and systematic reviews with meta-analyses). Results from these studies must demonstrate an odds ratio or relative risk of at least 2.0 or above in order to be meaningful. Anything between 1 and 2 is weak while >2 is
Consistency	moderate and >4 is considered strong. A relationship is repeatedly observed in all available studies.
Specificity	A factor influences specifically a particular outcome or population. The more specific an association between a factor and an effect, the greater the probability that it is causal.
Temporality	The cause must precede the outcome it is assumed to affect (e.g., smoking before the appearance of lung cancer). Outcome measured over time (longitudinal study).
Biological gradient (dose-response)	The outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory (e.g., the more cigarettes one smokes, the greater the chance of the cancer occurring).
Plausibility	The observed association can be plausibly explained by substantive matter (i.e., biologically possible)
Coherence	A causal conclusion should not fundamentally contradict present substantive knowledge. (Studies must not contradict each other.)
Experiment	Causation is more likely if evidence is based on randomized experiments or a systematic review of randomized experiments. However, these RCTs may not be ethically possible and thus prospective rather than experimental studies, such as cohort studies, may be the highest level of evidence available.
Analogy	For analogous exposures & outcomes an effect has already been shown (e.g., Effects first demonstrated on animals or an effect previously occurring on humans such as the effects of thalidomide on a fetus during pregnancy).

Source: Lavigne SE. From Evidence to Causality: How Do We Determine Causality? [Online-college]. 2018. From: https://www.dentalcare.com/en-us/archived-course-pdf?searchKey=causality

Periodontitis world perspective

The intricate relationship between DM and oral health has gained increasing attention in global health discussions over the past decades. The expert panel at the 2013 joint workshop of the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) has contributed to this presumed connection through a series of statements. The proceedings highlight the association of periodontitis and systemic diseases but do not imply causality. In 2018 the insights from this EFP/APP workshop were updated and extended by a collaboration between the EFP and International Diabetes Federation (IDF) further addressing the association between periodontitis and DM.

In the proceedings of this latter workshop, it is suggested that severe periodontitis can negatively impact blood glucose regulation, potentially leading to poorer DM outcomes.²⁴ These findings have influenced global discussions on DM and oral health and have contributed to the recommendations of clinical practice guidelines. For instance, (uncontrolled) DM is recognized by the AAP and EFP periodontitis classification as a risk factor for periodontal

disease and is incorporated as a 'grading' component. ^{25,26} Reflecting this global shift, countries like the Netherlands have integrated DM into healthcare guidelines for general physicians. The standard of the Dutch College of General Practitioners (NHG) emphasize the need for good oral health in the maintenance of DM type II. Additionally, the Dutch Diabetes Federation (NDF) has developed a toolkit to integrate oral health into comprehensive DM care. DM is also recognized as a key factor in the Dutch classification of periodontal diseases. ²⁷ This approach exemplifies a growing trend toward medical-dental integration, where systemic conditions like DM play a role in periodontal diagnosis and management.

Already in the first EFP-APP workshop on periodontitis and systemic diseases emphasis was given to the association between periodontitis and atherosclerotic cardiovascular disease.²⁸ In the light of this, the EFP extended their collaborations in 2019 with the World Heart Federation (WHF).²⁹ The proceedings of this Perio-Cardio Workshop was presented in a consensus report which provided recommendations for oral health professionals regarding the dental practice in people with cardiovascular diseases and events (CVD/CVE). For instance, patients with periodontitis should be advised that they are at higher risk for CVE such as myocardial infarction or stroke, and as such, they should actively manage all their cardiovascular risk factors. Patients with periodontitis and a diagnosis of CVD/CVE should be informed that they may be at higher risk for subsequent CVD/CVE complications. Therefore, they should regularly adhere to the recommended dental check-ups and care.²⁹ However, a recent study found that decrease of the inflammatory burden after periodontal treatment did not improve the endothelial function, or other cardiovascular parameters after one-year follow-up.³⁰ Furthermore, a recent Cochrane review concluded that the available literature does not provide sufficient evidence to support or refute the potential benefits of periodontitis treatment in the primary and secondary prevention of CVD.31

To bring gathered information back to daily medical general practice the EFP organized a workshop in 2023 together with the European arm of the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA Europe).³² The resulting consensus report underscores the importance of closer collaboration with family doctors, other health professionals, and healthcare funders for early detection and the prevention of non-communicable diseases (NCDs).³² This initiative highlights the growing recognition of periodontitis not just as a localized oral concern, but as part of the larger spectrum of NCDs that affect overall health. Moreover, a 2024 opinion paper published in Periodontology 2000 reinforced this view, proposing that periodontitis should be regarded as a systemic disease, aligning it with other chronic NCDs.³³

Caries world perspective

According to the WHO Global Oral Health Status Report³⁴ caries is the most prevalent oral disease. The prevalence estimate for untreated caries of permanent teeth is around 2 billion cases and of deciduous teeth with about 510 million cases.³⁴ Once there is established tooth decay, the carious process cannot be reversed, and management of the condition may include several stages of (restorative) treatment.³⁵

The relationship between dental caries and oral health has increasingly expanded to include its connection with DM. While this relationship has been less prominently addressed in the literature than periodontal disease, the available evidence stresses the need to consider the broader systemic impacts on oral health. The WHO state on their website that "there is a causal link between high sugar consumption, DM, obesity, and dental caries", illustrating how risk factors as lifestyle and dietary factors tied to DM directly affect caries risk. Findings from an expert panel have provided a more nuanced view, suggesting that the link may not be as direct as the WHO has stated. During the 2021 joint workshop, the EFP and the European

Organization for Caries Research (ORCA) reviewed several common acquired risk factors for both caries and periodontal diseases. These included hyposalivation, rheumatoid arthritis, smoking, and obesity, and undiagnosed or sub-optimally controlled DM, with only the latter noted as a contributing factor.³⁷

Interestingly, the executive councils of ORCA and the European Federation of Conservative Dentistry (EFCD) in their 2021 consensus statements on caries management did not identify DM as a direct risk factor. Instead, DM was categorized as 'medical condition'. The consequent recommendation was that dental care professionals must monitor patients with systemic conditions affecting plaque control, diet, and salivation more closely. The rationale provided was that these factors collectively increase the risk of caries development.³⁸

Oral health and diabetes

The above-mentioned EFP workshops and consensus reports and recommendations^{23,24,28,32,37} are widely spread via the different associations and collaborating parties to dental care professionals. Although the recommendations are generally accepted, most rely on observed associations, and it is therefore essential to remain critical of the extent to which the oral condition directly affects DM and vice versa. For this reason, Chapter 3 of this thesis was initiated in order to estimate the strength of the association of periodontal disease and DM as reported in systematic reviews (SRs). This synopsis of synthesis (or meta-review) primarily evaluated the presence or absence of DM in periodontal patients compared to non-periodontally diseased individuals. After screening of 487 titles and abstracts, four SRs with seven meta-analyses were found eligible to be included. For the majority (57%) of the reported RRs and ORs the estimated magnitude of the association of periodontal disease and DM was considered small. For 29% the association was considered to be negligible. Subanalyses showed that factors such as gender, severity of periodontal disease, smoking status, and geographical location were associated with the observed relationship. By applying the Bradford Hill criteria on the various aspect of the observed relationship a definitive confirmation of causality was not established due to the fact that 3 out of 9 criteria namely consistency, biological gradient, and plausibility, could not be satisfied. Consequently, it was concluded that with moderate certainty, a negligible to small association between periodontal disease and DM was identified, without support of causality. This interpretation of a limited association is not in line with several stronger conclusions and recommendations such as the ones from the EFP.

The joint workshop of the EFP with the International Diabetes Federation (IDF) in 2017 updated the evidence from the international EFP/AAP workshop in 2012. The first consensus rapport (Chapple et al. 2013) based their recommendations of the SR by Borgnakke et al. 39 and the latest consensus report (Sanz et al. 2018) on Graziani et al.; 40 which in fact was a revision of Borgnakke et al.³⁹ Both underlying papers of the two consensus reports are not included in the analysis as presented in **Chapter 3**. The reason for this is that these two SRs^{39,40} did not fulfill the eligibility criteria as both did not perform a meta-analysis and therefore lacked a measure of association. Due to the lack of pooled data, it was not possible to establish an overall estimation or interpret the magnitude of the effect based on Cohens d14 (see Table 1). Moreover, those two reviews 39,40 did not apply GRADE which is widely regarded as the tool to estimate the strength of the body of evidence. 41,42 GRADE is a systematic approach to rate the certainty of evidence in SRs and other evidence syntheses. 43 It is according to the guideline found in the Cochrane Handbook at present a recommended aspect of an SR.¹² The PRISMA 2020 guidelines⁴⁴ for SRs evaluating interventions also recommend that a method used to assess the certainty (or confidence) in the body of evidence for the outcome is part of the SR. Whereas the MOOSE guidelines⁴⁵ for SRs of observational studies do not include such a recommendation, this incongruity may be

explained by the fact that the MOOSE guidelines have not been updated in over two decades. In a paper by Bartold & Mariotti (2017)⁴⁶ entitled The Future of Periodontal-Systemic Associations a 'Disease Association Checklist' was introduced for a rational assessment of disease associations. Furthermore, these authors emphasize the importance of applying the Bradford-Hill criteria and the STROBE statement in any publication on periodontal-systemic observational associations. ^{46,47} In study presented in **Chapter 3** Cohens d (see Table 1)¹⁴ was used to interpret the reported ORs in the underlying SRs. The magnitude of the ORs suggests a negligible up to a small association between periodontitis and DM. This underscores the importance of critically assessing and interpreting the underlying evidence when drawing conclusions and formulate recommendations for guidelines.

It has also been suggested that apart from periodontal conditions DM can also adversely affect cardiovascular health. Both periodontitis and CVD are recognized as multifactorial conditions, with their development involving a complex interplay of various components such as genetics, microbial agents, inflammation, lifestyle and metabolic disorders. An extensive narrative review explores all potential hypotheses of this relation. This review highlights also the issue with surrogate markers. These markers may also introduce collider bias, a phenomenon that arises when two variables (e.g., the disease and the biomarker) influence a third variable (e.g., the likelihood of being included in a study). In this case, the selection of patients based on certain criteria (like a specific biomarker threshold or health condition) may inadvertently create a distorted relationship between variables. This limitation is relevant because a substantial number of studies primarily relied on surrogate biomarkers to evaluate the relationship, which may limit their ability to accurately capture the true extent of the association. Studies focusing on more direct parameters, such as Coronary Artery Calcium (CAC) scores found no significant association between CVD and periodontitis.

The strength of this relationship was explored in the synopsis of synthesis as presented in **Chapter 2**, which examined the association between periodontal disease and CVD/CVE as reported in existing SRs. The search was designed to retrieve all publication including both these diseases. Only studies evaluating the effect of periodontal disease on CVD/CVE were considered. Studies which for example also assessed comorbidities such as DM were therefore excluded. Independent screening of 446 reviews resulted in 19 eligible SRs. These were categorized into 13 reviews evaluating CVD and eight evaluating CVE. In total 27 meta-analysis were obtained. The majority (73%) of reported RRs and ORs were estimated to show a negligible magnitude of the association of periodontitis and CVD. For CVE 46% of the values of the reported measures of association were considered to be of small magnitude as emerging from 23 meta-analysis. Given these results and further analysis, a definitive confirmation of causality according to the Bradford Hill criteria (see Table 2) was not attainable. Consequently, with moderate certainty, a predominantly negligible to small magnitude of the association of periodontitis and CVD/CVE was identified.

This is in contrast with the conclusions of the EFP cardiovascular consensus paper²⁹ which report a significant association between periodontitis and cardiovascular diseases. This position paper outlines the findings of a workshop jointly organized by the EFP and the World Heart Federation (WHF).²⁹ The workshop reviewed and updated the existing epidemiological evidence linking periodontitis and CVD, exploring the underlying mechanistic connections, and examining the effects of periodontal therapy on cardiovascular and surrogate outcomes. Additionally, the risks and complications of periodontal treatment in patients on antithrombotic therapy were evaluated, with emerging recommendations provided for dentists, physicians, and patients visiting both the dental and medical practices. These findings were primarily based on an updated SR⁵³ that solely presented the results in a descriptive manner and did not include a meta-analysis. This makes it impossible to provide an overall estimate or assess

the magnitude of the effect which is needed to translate the results into clinical relevance.⁵⁴ Additionally, the EFP highlighted evidence from a large Asian study utilizing the Taiwanese National Health Insurance Research Database, which reported a significant association between periodontitis and heart failure, with a HR of 1.31.55 Yet a HR of 1.31 corresponds to a small effect size¹⁵ (see Table 1). This suggests that while periodontal inflammation may contribute to cardiovascular health issues, its impact is smaller than often portrayed. Moreover, causality between periodontitis and CVD/CVE remains elusive. This presumption is supported by a recent position paper published by the Canadian Dental Hygienist Association (CDHA) in which it was reported that there is insufficient evidence for a causal relationship between periodontitis and CVD.56 Given that individuals with periodontitis frequently exhibit one or more systemic diseases⁵⁷ or comorbidities,⁵⁸ it is reasonable to hypothesize that the observed associations between periodontitis CVD/CVE, and DM may partially overlap due to shared risk factors. While the link between periodontitis and CVD or CVE is well-documented, the association is of relatively small magnitude, and current evidence remains insufficient to establish a causal relationship. Notably, as this connection appears to be partially mediated by DM, it suggests an indirect association between periodontitis and CVD/CVE.

Diabetes and oral health Periodontitis

The proposed biological pathway explaining the association between DM to oral health is primarily attributed to hyperglycemia-induced changes. Elevated blood sugar levels can impair the immune response, making it more difficult for the host to combat bacterial infections in the periodontal tissues.⁵⁹ This not only increases the risk and severity of periodontal disease but also exacerbates the DM related conditions. 60 In relation to the latter, periodontal therapy is often proposed as an adjunctive treatment to help improve glycemic outcomes. 61 Reversely it is unclear if periodontal therapy by itself is as effective for DM periodontitis patients as compared to non-DM periodontitis patients. The available scientific evidence of the potential impact of DM on periodontal treatment outcomes in periodontitis patients undergoing non-surgical periodontal therapy (NSPT) was examined in an SR presented in Chapter 5. The inclusion criterion was the availability of data for a group of patients with both DM and periodontitis and a group with solely periodontitis. Screening of the 3574 papers resulted in 32 eligible publications, which reported 30 unique studies. Meta-analyses showed no differences of means (DiffM) with respect to incremental changes following NSPT from baseline to evaluation between the DM and non-DM groups for clinical attachment level (CAL) and periodontal probing depth (PPD). These findings were deemed conclusive and reliable based on the Trial Sequential Analysis (TSA) of the meta-analysis data. The required information size (RIS) was reached as the cumulative sample size was large enough, for PPD and CAL. Both did not cross the two side Z boundary (Z= 1.96, P<0.05)62 corresponding to a non-significant difference. Consequently, the type 1 error (false positive) could not be ruled as the 0-hypothesis, was adopted.

While it is generally suggested that poorly controlled DM impacts periodontal (treatment) outcomes, ²³ interestingly, significant differences in primary outcomes were observed only for CAL (DiffM=0.08, p=0.01) in patients with poorly controlled DM. Based on clinical relevance scale for interpreting mean differences in CAL¹⁷ this was considered as 'zero' effect (see Table 1). No significant differences were found for PPD (DiffM=0.07, p=0.29) for poorly controlled DM. The TSA performed for poorly controlled DM regarding PPD showed that the cumulative Z curves crossed the futility boundary already after 2 studies were included. The futility was confirmed after 3 studies were included when the sample size exceeded the RIS. It can therefore be confidently inferred that the effect of NSPT between the groups was comparable. The user-

defined mean difference effect was set at 0.31, with a Type 1 Error of 5.0 %, and a power of 80%. The estimated inconsistency was $I^2 = 75\%$, and the estimated diversity was $D^2 = 94\%$. In summary, the effect was conclusive and reliable and additional new data are unlikely to affect the reported summary effect. 63 In conclusion, DM does not significantly influence treatment outcomes in patients undergoing NSPT. This is in line with another SR which concluded that DM does not appear to affect short-term periodontal outcomes of NSPT.64 Periodontitis patients with DM can therefore be treated as effectively as non-DM patients when undergoing NSPT. The periodontal disease therapeutic guidelines 65,66 can be followed for successful periodontal treatment. These findings support the consensus report and guidelines of the joint workshop on periodontal diseases and DM by the IDF and the EFP²⁴ in which it was reported that clinical periodontal parameters improve following NSPT, also in people with poorly controlled DM. This consensus report by the IDF and the EFP does not provide any recommendation regarding the interpretation of the magnitude of the effect.²⁴ NSPT is often followed by supportive periodontal care (SPC), which has a positive impact on periodontal stability. Annual tooth loss during SPC has been found to be significantly higher in drop-out patients compared to partially or fully compliant patients, also after adjustment for DM.67

The influence of DM on the periodontal condition is examined in the meta review as presented in **Chapter 4**. SRs evaluating the periodontal condition of periodontitis patients with DM versus non-DM were included. The primary outcome parameters of interest were CAL and PPD. The search resulted in 488 unique titles and abstracts. After full text reading seven SRs were eligible for inclusion, encompassing a total of 154 underlying clinical studies. Of these, 79 studies involved DM type I, 50 DM type II, 23 both types of DM and 2 studies gave no specification about DM types. Regarding CALoss the magnitude of the DiffM was estimated to be small to moderate for DM I (ranging from 0.26-0.652) and substantial for DM II (0.691-1.00) and DM I/II (0.612-0.78). For CALevel the magnitude of the DiffM was moderate to substantial (0.468-0.82) for DM I and substantial for DM II (0.89). For PPD the DiffM were estimated to be zero to moderate for DM I (0.11-0.55), moderate to substantial for DM II (0.46-0.61) and small to substantial for DM I/II (0.346-0.67). For interpretation see Table 1.

Chapter 4 and 5 have drawn conclusions on SRs that include various clinical studies. It is also important to acknowledge the limitations inherent with these studies. For example, measurements errors that may occur in probing depth measurements. Periodontal probes are the main instruments to assess periodontal parameters, such as bleeding tendency (BOP), PPD and CAL. It is known that differences in probe type could introduce measurement errors when comparing periodontal data within and between epidemiological studies. 68 Inconsistent probe usage may lead to either under or overestimation of PPD and CAL, resulting in inaccuracies in periodontal assessments. 69 Furthermore, periodontal probes have shown significant variation in dimensions (probe tine diameter and calibration of markings)⁷⁰ and the pressure applied during probing can be influenced by design of the probe handle, affecting accuracy. Moreover, periodontal screening often involves subjective interpretation of clinical signs, which may result in discrepancies in diagnosis and classification. Patient-related factors, such as variations in gingival anatomy, tooth morphology, and oral hygiene practices, can also influence the accuracy of periodontal measurements. Patient discomfort or anxiety during probing may also affect the reliability of periodontal screening results.72-75 All such factors may contribute to variations in probe recordings, influencing the sequence from clinical measurements to data used in clinical trials, SRs, meta-reviews, and ultimately this thesis.

Caries

The scientific literature, in addition to periodontitis, also suggests, an effect of DM on caries. A recent SR found that individuals with DM had significantly lower unstimulated and stimulated salivary flow rates. A Saliva plays a critical role in maintaining oral health by neutralizing acidic products of oral bacteria and providing essential minerals for enamel remineralization. Reduced salivary flow can lead to an increased risk of tooth decay, oral infections, and discomfort. On top, it is suggested that insulin deficiency in DM may lead to hyposalivation and elevated salivary glucose levels. However, the detailed biological pathway between oral dryness and DM is unclear. Patients suffering from DM type II are relatively older and it is likely that age also plays a role in this mechanism. Medication, such as anti-hypertensives or psychotropic drugs, are also risk factors for hyposalivation and could therefore act as an important confounder in evaluating the relationship between DM and caries.

The WHO recommends the DMF (decayed-missing-filled) index for recording caries in epidemiological studies.80 Two SRs81,82 have been performed to evaluate the prevalence of dental caries in DM patients. Both studies present conclusions of a higher dental caries risk among children and adolescents with DM type I. These two SRs did however not focus on adults and did not include DMF index scores. Therefore, the SR as presented in Chapter 6 evaluated DMF scores for determining caries experience in observational studies comparing adults with DM to non-DM. Screening and selection of titles and abstract and subsequent full-text reading identified 13 eligible studies. Only those that reported on participants without other co-mobilities were included. To summarize and interpret the findings the WHO severity criteria for population levels of DMFT (decayed-missed-filled-teeth) were used. As these criteria are currently not available for DMFS (decayed-missed-filled-surfaces) scores, these DMFT severity levels were converted for this interpretation by the authors of the review, see Table 3. The meta-analysis reported a significant difference of means (DiffM) of 3.01 for DMFT (95% CI: [1.47;4.54], p=0.0001) and a DiffM of 10.30 for DMFS (95% CI: [8.50;12.11], p<0.00001). The results indicate a higher DMF index score for patients with DM as compared to non-DM individuals. When interpreting the magnitude of the effect as degree of caries experience this can be considered as small.80 The subgroup analysis showed that this was irrespective of the type of DM. Another SR already conducted in 2020 excluded studies that evaluated both type I and II of DM. They found that only the population with type I DM had significantly higher DMFT scores as compared to controls (DiffM: -0.55, 95% CI: [-1.10;-0.01]), but no difference was found between type II and non-DM (DiffM: -5.16, 95% CI: [10.62;0.30]).81 Further it is suggested albeit limited in certainty that there are indications that individuals with undiagnosed or poorly controlled type I DM may have an elevated risk of caries initiation and progression. 83 This seems a topic for additional research in the future. Although DMF indices can provide relevant data, the overall score may include teeth and surfaces that have been lost for reasons other than caries such as periodontitis. As a result, the scores may not accurately reflect the true burden of caries and could potentially lead to an overestimation of its prevalence and severity.84

Table 3Interpretation of the DMFT indices and converted DMFS index

	DMFT (32 teeth) ^{s0}	Converted DMFS (148 surfaces)
Very low	<5.0	<23
Low	5.0-8.9	23-41
Moderate	9.0-13.9	42-64
High	>13.9	>64

Endodontic treatment

It has recently been suggested that dentists must investigate the presence of DM in those patients in whom a high frequency of root canal treatment is observed. To improve the understanding of the active role of DM as an etiological factor for endodontic treatment as a surrogate parameter for extensive tooth decay a retrospective case control analysis was performed and presented in **Chapter 7**. A convenience sample of 233 DM and 233 non-DM periodontitis patients were matched based on age, gender and year of intake. The rationale for this study population is that for periodontitis patients usually a full set of radiographs is available for diagnosis and treatment planning. Also, the prevalence of DM was considered to be higher among periodontitis patients than among a random patient sample. Based on this retrospective analysis no statistically significant difference was found in the mean percentage of endodontically treated teeth.

Approximately 50% of the global adult population is affected by apical periodontitis (AP) in at least one tooth.⁸⁷ In Europe, the prevalence of AP affects 61% of individuals and 14% of teeth, with its incidence increasing with age.⁸⁸ AP is a pathophysiological inflammatory process primarily instigated by microbial infection.⁸⁹ Bacterial infiltration of the root canal system typically occurs when the pulp is necrotic or has been previously removed during endodontic procedures. In certain conditions, such as acute and chronic abscesses, the infection may extend into the periradicular tissues.⁹⁰

DM has the potential to influence both periodontal and periapical tissues through various mechanisms, including alterations in the oral microbiota, impaired neutrophil function, altered immune responses, cytokine production, and the induction of oxidative stress. 91 Moreover, DM is associated with increased inflammation and tissue degeneration, particularly post-dental interventions. 92 In cases of hyperglycemia, an increased inflammatory state could result in a diminished healing of apical tissues.93 A positive correlation between the presence of AP, the size of the periapical lesion and elevated HbA1c and serum glucose levels has been observed.94 A recent SR found, although with marginal significance, that the prevalence of root-filled teeth in patients with DM is nearly double compared with the general population. 85 Clinicians should also be aware of a potentially higher incidence of periapical abscesses in obese patients.95 Although root canal treatment remains an effective conservative treatment for individuals with DM, a significantly lower rate of healing has been observed in people with DM, suggesting that regular follow-ups are necessary to monitor the healing process. 96 Supporting this, AP after root canal treatment is more prevalent in type II DM patients compared to control groups.97 Furthermore, in cases where preoperative AP is present, DM may exacerbate the development of AP in endodontically treated teeth.98 This exacerbation can be attributed to the heightened inflammatory state observed around the peri-apex in DM patients. 99 Patients with periodontitis are also more likely to develop AP.100 Furthermore, with respect to periodontal bone loss, teeth with an endodontic treatment tend to experience more bone loss compared to untreated contra-laterals. Additionally, those restored with an endodontic post often exhibit more angular bony defects. 101,102 However, studies examining the relationship between AP and DM demonstrate considerable heterogeneity and methodological challenges, leading to a conclusion that a positive association between DM and AP has limited evidence. 103

Tooth loss

In addition, **Chapter 7** also examined the mean number of teeth in relation to DM. The analysis revealed no statistically significant difference in the mean number of teeth between the 233 DM periodontitis patients compared to the 233 non-DM periodontitis patients. Conversely, in **Chapter 8**, a small but significant higher risk of tooth loss for DM patients were found. The SR

presented in this chapter, included 10 studies, which primarily evaluate the number of teeth in DM patients and in non-DM. The meta-analysis found a significant RR of 1.63 (p<0.00001) with a 95% CI [1.33:2.00]. In the DM population poorer glycemic control, as well as the Asian or South America ethnicity, were associated with numerically higher risks of tooth loss. It is suggested that Asians are particularly susceptible to periodontitis¹⁰⁴ and DM prevalence has also been reported to be higher in Asians.¹⁰⁵ The variation in the summarized findings may be partly due to differences in the population samples among the included studies and the methods used in each analysis. A possible explanation of the non-significant findings in Chapter 7 may be due to the fact that the sample does not fully represent the DM population but was restricted to periodontitis patients who had been referred by their general dentist to a specialized clinic for periodontology. Whereas the studies in Chapter 8 included diverse study designs and populations, potentially capturing a more comprehensive and generic view of the relationship between DM and tooth loss. From a methodological point of view evaluating number of teeth can be confusing as studies often do not report what is considered as the reference number of teeth. According to the WHO the standard reference number of teeth is 32.80 However, some studies used a baseline reference of 28 teeth, as they excluded the wisdom teeth which could introduce a misrepresentation when extracting data from these studies. In Chapter 8, there was a non-significant numerical difference in the RR of tooth loss between studies evaluating 28 teeth (RR = 1.64) versus 32 teeth (RR=1.51), although the 95% Ols overlap [1.29;2.08] and [1.45;1.58], respectively. Both RRs can be interpreted as a small risk (see Table 1).13 The numerically lower risk with DM for 32 teeth may be related to the prophylactic removal of wisdom teeth.

Edentulism

The ultimate outcome parameter for tooth loss is edentulism.³⁴ The available evidence concerning the prevalence of edentulism among DM patients compared to non-DM people was systematically and critically appraised as presented in Chapter 9. The inclusion criteria were observational studies conducted in human subjects ≥18 years old with the primary aim of investigating the prevalence of edentulism among DM patients. Studies that reported on edentulism as a side observation were not considered appropriate in order to avoid bias introduced through sample selection. Independent screening of 2085 unique titles and abstracts revealed seven publications that met the strict eligibility criteria. The study size ranged from 293 to 15,943 participants. Data from all seven studies were suitable for metaanalysis. Overall, 8.3% of the studied populations were edentulous. The weighted mean prevalence of edentulism among DM and non-DM was 14.0% and 7.1%, respectively. The overall OR for DM patients to be edentulous as compared to non-DM was 2.39 (95% CI [1.73;3.28], p<0.00001) which was interpreted as small (see Table 1).14 The findings of the SR in Chapter 9 suggest with a moderate certainty a small but significant risk of edentulism for DM patients. Based on the WHO global oral health status report edentulism is estimated with 350 million cases in 2019.34 The Global Burden of Disease (GBD) study assessed the prevalence and burden of severe periodontitis and edentulism in 2021 with projections up to 2050.106 The prevalence of edentulism was estimated at 4.11% in 2021.83 With a growing and aging population, periodontitis and edentulism are expected to affect an increasing number of people. However, the current GBD definition for severe periodontitis does not account for tooth loss which could lead to an underestimation of its true burden. According to the DM Atlas¹⁰⁷ 537 million adults (20-79 years) are living with DM. This number is predicted to rise to 643 million by 2030 and 783 million by 2045.107 As both DM and edentulism and also periodontitis are estimated to grow, it is of interest whether the ratio between the diseases will maintain or gradually change. Therefore, it remains a topic for further epidemiological research.

Data spinning

The results of the meta-reviews in Chapter 2 and 3 confirm the existence of negligible to small associations and insufficient evidence to satisfy the Bradford Hill criteria necessary to support the presumption of a causal relationship. Therefore, caution must be exercised regarding data spinning—an analytical practice where researchers emphasize specific results, often through selective reporting or manipulating data presentation, to create a more favorable or impactful narrative. Data spinning can lead to misinterpretation of findings and overstate the significance of results, potentially masking the true effect sizes, association strength and/ or clinical relevance. In addition, publication bias may also play a role, as most publications originate from dental journals, while medical journals appear to allocate limited focus to this topic.7 This can skew perceptions of treatment efficacy and may misguide clinical practice and decision-making. A recent scoping review reported that the practice of spin is widespread in dental scientific literature. 108 Current review methodologies in the peer review process for scientific publications make minimal attempts to mitigate this effect.¹⁰⁹ Consensus papers and guidelines are not strict in applying interpretation strategies which implies a direct impact and therefore risk to clinical decision making in daily practice. Dental care professionals should inform patients about the association between oral health and DM but should not overestimate or exaggerate the strength of this relationship. Moreover, using fear as a motivator in healthcare is a complex and multifaceted topic. 113 Thus, transparent reporting and careful consideration of both statistical significance and effect size or strength metrics are of importance to ensure that the results reflect an accurate and reliable understanding of the impact of findings in real-world settings.

Risk factors

The WHO defines a risk factor as "any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury". ¹¹⁴ In several EFP workshops with the IDF, WHF and WONCA Europe^{23,24,29,32} multiple risk factors are mentioned such as: smoking, exercise, excess weight, blood pressure, lipid and glucose management, sufficient periodontal therapy and periodontal maintenance, DM, obesity, smoking, hypertension, hyperlipidaemia and hyperglycaemia. However, current prevention concepts focus primarily on the presence of individual diseases or conditions and potential disease-related risks, often without considering the patient as a whole. ¹¹⁵ Looking ahead, it is important to adopt an individualized, prevention-oriented, and patient-centered approach to dental care, addressing the specific risks and needs of each patient. ^{115,116}

The EFP S3-level clinical practice guidelines stages I/II and IV periodontitis⁶⁵ are considered as the worldwide standard. They present a 4-point stepwise treatment planning and highlight selected specific clinical recommendations including risk factors.⁶⁵ In the description of steps 2 and 3 which concern active periodontal treatment, no specific recommendations for the mentioned risk factors were provided. However, in step 1 and 4 the following guidance is given:

Step 1: Guiding behaviour change by motivating the patient

- Control of risk factors is recommended as part of the first step of treatment.
- Tobacco smoking cessation interventions are recommended as part of the first step of treatment.
- DM control interventions are necessary.
- It is not known if increasing the physical activity has an impact.
- It is not known if reducing weight through dietary and lifestyle has an impact.

Step 4 Supportive periodontal care (SPC)

- Tobacco smoking cessation interventions needs to be implemented.
- DM control interventions are necessary.
- It is not known if increasing the physical activity and reducing weight through dietary and lifestyle modification has an impact in patients in supportive periodontal care.

The present thesis did not evaluate smoking as a risk factor for periodontitis. The results of the studies included in the chapters do not specifically support the necessity of DM control interventions to improve the outcomes of NSPT. This thesis does not provide data on the risk associated with DM control and periodontal stability. It does, however, suggest that DM control interventions may be necessary in relation to the increased risks of caries and tooth loss. The impact of appropriate interventions on the progression of periodontitis and caries still needs to be evaluated.

CONCLUSION

Based on the research presented in this thesis it appears that DM is a small but relevant risk factor in dental and oral health. For DM patients with caries, a conservative treatment approach is recommended to preserve teeth, supplemented with preventive measures to maintain oral health. DM patients with periodontitis can successfully be treated according to the stages I/II and IV guidelines for periodontitis. The objective in principle should be to improve oral health and not primarily to improve their DM markers. Regardless of the DM status the main focus of professional dental care should continue to be on emphasizing the importance of self-performed oral care and ensuring regular dental check-ups for all individuals.

PRACTICAL IMPLICATIONS

Recommendations for oral health professionals

Dental care clinicians should inform patients about the association between oral health and DM but should not overestimate or exaggerate the strength of this relationship. DM patients with caries and/or periodontitis should be treated according to the guidelines primarily for maintaining teeth. 'Prevention' of oral diseases, caries and/or periodontitis should be the focus what starts with optimal daily self-care at home.

Recommendations for researchers

In studies reporting statistical significance, it is important to provide an estimate of clinical relevance by including effect sizes and corresponding confidence intervals, or alternatively, offering a detailed interpretation of the strength and robustness of the evidence regarding the association, correlation, risk, or treatment effect.

REFERENCES

- 1. Coelho AS, Amaro IF, Caramelo F, et al. Dental caries, diabetes mellitus, metabolic control and diabetes duration: A systematic review and meta-analysis. *Journal of Esthetic and Restorative Dentistry.* 2020;32(3):291-309. doi:10.1111/jerd.12562
- 2. Sun S, Mao Z, Wang H. Relationship between periodontitis and diabetes: a bibliometrics analysis. *Ann Transl Med.* 2022;10(7):401-401. doi:10.21037/atm-22-1067
- 3. González-Moles MÁ, Ramos-García P. State of evidence on oral health problems in diabetic patients: A critical review of the literature. *J Clin Med.* 2021;10(22). doi:10.3390/jcm10225383
- 4. Merriam-Webster. Definition bidirectional. Accessed November 11, 2024. https://www.merriam-webster.com/dictionary/bidirectional#:~:text=two%20opposite%20directions-,Medical%20Definition,flow%20of%20 materials%20in%20axons).
- 5. Siddiqi A, Zafar S, Sharma A, Quaranta A. Diabetes mellitus and periodontal disease: The call for interprofessional education and interprofessional collaborative care A systematic review of the literature. *J Interprof Care*. 2022;36(1):93-101. doi:10.1080/13561820.2020.1825354
- Poudel P, Griffiths R, Wong VW, et al. Perceptions and practices of general practitioners on providing oral health care
 to people with diabetes A qualitative study. BMC Fam Pract. 2020;21(1). doi:10.1186/s12875-020-1102-9
- 7. Sun S, Mao Z, Wang H. Relationship between periodontitis and diabetes: a bibliometrics analysis. *Ann Transl Med.* 2022;10(7):401-401. doi:10.21037/atm-22-1067
- 8. Gao B, Wu J, Lv K, Shen C, Yao H. Visualized analysis of hotspots and frontiers in diabetes-associated periodontal disease research: a bibliometric study. *Ann Transl Med.* 2022;10(24):1305-1305. doi:10.21037/atm-22-2443
- 9. DS Moore, GP MacCabe, BA Craig. Introduction to the Practice of Statistics. 9th ed. W.H.Freeman & Co Ltd; 2017.
- 10. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. N Eng J Med. 1987;317:426-432.
- 11. Greenland S, Senn SJ, Rothman KJ, et al. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol.* 2016;31(4):337-350. doi:10.1007/s10654-016-0149-3
- 12. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (Updated August 2023). Cochrane; 2023.
- 13. Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. *Commun Stat Theory Methods*. 2017;46(14):6774-6781. doi:10.1080/03610926.2015.1134575
- 14. Chen H, Cohen P, Chen S. How Big is a Big Odds Ratio? Interpreting the Magnitudes of Odds Ratios in Epidemiological Studies. Communications in Statistics—simulation and Computation®. 2010;39(4):860-864.
- 15. Lu Y, Wang W, Huang Y, Chen H. How big is a big hazard ratio in clinical trials? *Int J Clin Trials*. 2023;10(3):195-200. doi:10.18203/2349-3259.ijct20232191
- 16. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed.: 1988.
- 17. Smiley CJ, Tracy SL, Abt E, et al. Evidence-based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. *Journal of the American Dental Association*. 2015;146(7):525-535. doi:10.1016/j.adaj.2015.01.026
- 18. Sullivan GM, Feinn R. Using Effect Size—or Why the P Value Is Not Enough. *J Grad Med Educ.* 2012;4(3):279-282. doi:10.4300/jgme-d-12-00156.1
- Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation

 Determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-735. doi:10.1016/j.jclinepi.2013.02.003
- 20. Hill AB. The Environment and Disease: Association or Causation? In: *Proceedings of the Royal Society of Medicine.*; 1965:295-300.
- 21. Ioannidis JPA. Why most published research findings are false. In: *Getting to Good: Research Integrity in the Biomedical Sciences*. Springer International Publishing; 2018:2-8. doi:10.1371/journal.pmed.0020124
- 22. Beck JD, Papapanou PN, Philips KH, Offenbacher S. Periodontal Medicine: 100 Years of Progress. *J Dent Res.* 2019;98(10):1053-1062. doi:10.1177/0022034519846113
- 23. Chapple IL, Genco R. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol.* 2013;84(4-s):S106-S112. doi:10.1902/JOP.2013.1340011
- 24. Sanz M, Ceriello A, Buysschaert M, et al. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. *Diabetes Res Clin Pract.* 2018;137:231-241. doi:10.1016/J.DIABRES.2017.12.001
- 25. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. In: *Journal of Clinical Periodontology.* Vol 45. Blackwell Munksgaard; 2018:S162-S170. doi:10.1111/jcpe.12946
- 26. Caton JG, Armitage G, Berglundh T, et al. A new classification scheme for periodontal and peri-implant diseases and conditions Introduction and key changes from the 1999 classification. *J Periodontol.* 2018;89(S1):S1-S8. doi:10.1002/JPER.18-0157

- Nederlandse Vereniging voor Parodontologie. De Nieuwe Paro-classificatie Aan de slag met 'staging' en 'grading.'
 Accessed December 28, 2024. https://www.nvvp.org/voor-professionals/de-nieuwe-paro-classificatie
- 28. Tonetti MS, Van Dyke TE. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAPWorkshop on Periodontitis and Systemic Diseases. *J Periodontol.* 2013;84(4S). doi:10.1902/jop.2013.1340019
- 29. Sanz M, Marco del Castillo A, Jepsen S, et al. Periodontitis and cardiovascular diseases: Consensus report. *J Clin Periodontol*. 2020;47(3):268-288. doi:10.1111/jcpe.13189
- 30. Donders HCM, Veth EO, Edens MA, van 't Hof AWJ, de Lange J, Loos BG. The Effect of Periodontal Treatment on the Reactive Hyperemia Index. A 1-Year Follow-Up Pilot Study. *Front Cardiovasc Med.* 2022;9. doi:10.3389/fovm.2022.851397
- 31. Ye Z, Cao Y, Miao C, et al. Periodontal therapy for primary or secondary prevention of cardiovascular disease in people with periodontitis. *Cochrane Database of Systematic Reviews*. 2022;2022(10). doi:10.1002/14651858.CD009197. pub5
- 32. Herrera D, Sanz M, Shapira L, et al. Association between periodontal diseases and cardiovascular diseases, diabetes and respiratory diseases: Consensus report of the Joint Workshop by the European Federation of Periodontology (EFP) and the European arm of the World Organization of Family Doctors (WONCA Europe). *J Clin Periodontol.* 2023;50(6):819-841. doi:10.1111/jcpe.13807
- 33. Villoria GEM, Fischer RG, Tinoco EMB, Meyle J, Loos BG. Periodontal disease: A systemic condition. *Periodontol* 2000. Published online October 1, 2024. doi:10.1111/prd.12616
- 34. World Health Organization. Global Oral Health Status Report: Towards Universal Health Coverage for Oral Health by 2030.; 2022. http://apps.who.int/bookorders.
- 35. The Economist Group 2024. Time to Put Your Money Where Your Mouth Is: Addressing Inequalities in Oral Health.; 2024.
- 36. World Health Organization. Oral Health. March 13, 2023. Accessed January 21, 2025. https://www.who.int/news-room/fact-sheets/detail/oral-health#:~:text=There%20is%20also%20a%20causal%20link%20between%20 the,the%20poor%20and%20socially%20disadvantaged%20members%20of%20society.
- 37. Chapple ILC, Bouchard P, Cagetti MG, et al. Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. *J Clin Periodontol.* 2017;44:S39-S51. doi:10.1111/jcpe.12685
- 38. Huysmans MC, Fontana M, Lussi A, et al. European Organisation for Caries Research and the European Federation of Conservative Dentistry Consensus Report on Clinical Recommendations for Caries Diagnosis: Paper III Caries Diagnosis at the Individual Level. *Caries Res.* Published online May 31, 2024;521–532. doi:10.1159/000539427
- 39. Borgnakke WS, Ylöstalo P V., Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: Systematic review of epidemiologic observational evidence. *J Clin Periodontol*. 2013;40(SUPPL. 14).
- 40. Graziani F, Gennai S, Solini A, Petrini M. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes An update of the EFP-AAP review. *J Clin Periodontol.* 2018;45(2):167-187. doi:10.1111/jcpe.12837
- 41. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/BMJ.39489.470347.AD
- 42. GRADE home. Accessed December 23, 2023. https://www.gradeworkinggroup.org/
- 43. Shaheen N, Shaheen A, Ramadan A, et al. Appraising systematic reviews: a comprehensive guide to ensuring validity and reliability. *Front Res Metr Anal.* 2023;8. doi:10.3389/frma.2023.1268045
- 44. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *The BMJ*. 2021;372. doi:10.1136/bmj.n71
- 45. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. JAMA Surg. 2021;156(8):787-788. doi:10.1001/jamasurg.2021.0522
- 46. Mark Bartold P, Mariotti A. The Future of Periodontal-Systemic Associations: Raising the Standards. *Curr Oral Health Rep.* 2017;4(3):258-262. doi:10.1007/s40496-017-0150-2
- 47. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *Epidemiology*. 2007;18(6):805-835. doi:10.1097/EDE.0b013e3181577511
- 48. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *The Lancet*. 2005;366(9499):1809-1820. doi:10.1016/S0140-6736(05)67728-8
- 49. Zardawi F, Gul S, Abdulkareem A, Sha A, Yates J. Association Between Periodontal Disease and Atherosclerotic Cardiovascular Diseases: Revisited. *Front Cardiovasc Med.* 2021;7:401. doi:10.3389/FCVM.2020.625579/BIBTEX
- 50. Febbraio M, Roy CB, Levin L. Is There a Causal Link Between Periodontitis and Cardiovascular Disease? A Concise Review of Recent Findings. *Int Dent J.* 2022;72(1):37-51. doi:10.1016/j.identj.2021.07.006
- 51. Holmberg MJ, Andersen LW. Collider Bias. *JAMA*. 2022;327(13):1282-1283. doi:10.1001/jama.2022.1820
- 52. Donders HCM, Veth EO, van 't Hof AWJ, de Lange J, Loos BG. The association between periodontitis and cardiovascular risks in asymptomatic healthy patients. *International Journal of Cardiology: Cardiovascular Risk and Prevention*. 2021;11. doi:10.1016/j.ijcrp.2021.200110
- 53. Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. *J Clin Periodontol.* 2013;40:S70-84. doi:10.1111/

- jcpe.12062
- 54. Ferguson CJ. An Effect Size Primer: A Guide for Clinicians and Researchers. *Prof Psychol Res Pr.* 2009;40(5):532-538. doi:10.1037/a0015808
- 55. Chen DY, Lin CH, Chen YM, Chen HH. Risk of atrial fibrillation or flutter associated with periodontitis: A nationwide, population-based, cohort study. *PLoS One*. 2016;11(10). doi:10.1371/journal.pone.0165601
- 56. Lavigne SE, Forrest JL. An Umbrella Review of Systematic Reviews of the Evidence of a Causal Relationship between Periodontal Microbes and Respiratory Diseases: Position Paper from the Canadian Dental Hygienists Association. Vol 54.; 2020. www.dentalcare.com/en-us/professional-
- 57. Beukers NGFM, Su N, van der Heijden GJMG, Loos BG. Periodontitis is associated with multimorbidity in a large dental school population. *J Clin Periodontol*. 2023;50(12):1621-1632. doi:10.1111/jcpe.13870
- 58. Beukers NGFM, Loos BG, van der Heijden GJMG, Stamatelou E, Angelakis A, Su N. The Prevalence of Comorbidities in Individuals with Periodontitis in a Private Periodontal Referral Practice. *J Clin Med.* 2024;13(23):7410. doi:10.3390/jcm13237410
- 59. Taylor JJ, Preshaw PM, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. *J Clin Periodontol*. 2013;40(SUPPL. 14):S113-34. doi:10.1111/jcpe.12059
- 60. Taylor GW, Burt BA, Becker MP, et al. Severe Periodontitis and Risk for Poor Glycémie Control in Patients with Non-Insulin-Dependent Diabetes Mellitus. Vol 67.; 1996.
- 61. Teeuw WJ, Gerdes VE, Loos B. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. *Diabetes Care.* 2010;33(2):421-427.
- 62. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. *BMJ Open.* 6(8):e011890. doi:10.1136/bmjopen-2016
- 63. Thorlund K, Engstrøm J, Wetterslev J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). Copenhagen Trial Unit, 2011. Copenhagen, Denmark: Centre for Clinical Intervention Research. Published online 2017:1-119.
- 64. Hsu YT, Nair M, Angelov N, Lalla E, Lee CT. Impact of diabetes on clinical periodontal outcomes following non-surgical periodontal therapy. *J Clin Periodontol*. 2019;46(2):206–217.
- 65. Sanz M, Herrera D, Kebschull M, et al. *Treatment of Stage I-III Periodontitis—The EFP S3 Level Clinical Practice Guideline.* Vol 47. Blackwell Munksgaard; 2020. doi:10.1111/jcpe.13290
- 66. DAC van Strydonck, S Katsamakis, GA van der Weijden. Parodontale Screening, Diagnostiek En Behandeling in de Algemene Praktijk.
- 67. Kocher T, Lösler K, Pink C, Grabe HJ, Holtfreter B. Effect of Discontinuation of Supportive Periodontal Therapy on Periodontal Status—A Retrospective Study. *J Clin Periodontol*. Published online January 1, 2024. doi:10.1111/jcpe.14062
- 68. Holtfreter B, Alte D, Schwahn C, Desvarieux M, Kocher T. Effects of different manual periodontal probes on periodontal measurements. *J Clin Periodontol*. 2012;39(11):1032-1041. doi:10.1111/j.1600-051X.2012.01941.x
- 69. Al Shayeb KN, Turner W, Gillam DG. Periodontal probing: a review. Prim Dent J. 2014;3(3):25-29.
- 70. Van Der Zee E, Davies EH, Newman HN. Marking width, calibration from tip and tine diameter of periodontal probes. *J Clin Periodontol*. 1991;18:516–520.
- 71. van Weringh M, Barendregt D, Rosema N, et al. A thin or thick probe handle: does it make a difference? A thin or thick probe handle: does it make a difference? Int J Dent Hygiene. 2006;4:140-144.
- 72. Listgarten MA. Normal development, structure, physiology and repair of gingival epithelium. Oral Sci Rev. 1972;1:3-67.
- 73. Listgarten MA. Periodontal probing: What does it mean? JClin Periodontol. 1980;7:165-176.
- 74. Van Der Velden U, De Vries JH. Introduction of a new periodontal probe: the pressure probe. *J ClinPeriodontol.* 1978;5:188-197.
- 75. Theil EM, Heaney TG. The validity of periodontal probing as a method of measuring loss of attachment. *J Clin Periodontol.* 1991;18:648–653.
- 76. Marques RCR, da Silva JR, Vieira Lima CP, Stefani CM, Damé-Teixeira N. Salivary parameters of adults with diabetes mellitus: a systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2022;134(2):176-189. doi:10.1016/j.oooo.2022.03.001
- 77. Dodds M, Roland S, Edgar M, Thornhill M. Saliva A review of its role in maintaining oral health and preventing dental disease. *BDJ Team*. 2015;2(1-8). doi:10.1038/bdjteam.2015.123
- 78. Jawed M, Shahid SM, Qader SA, Azhar A. Dental caries in diabetes mellitus: Role of salivary flow rate and minerals. *J Diabetes Complications*. 2011;25(3):183-186. doi:10.1016/j.jdiacomp.2010.07.001
- 79. Leal SC, Bittar J, Portugal A, Falcão DP, Faber J, Zanotta P. Medication in elderly people: Its influence on salivary pattern, signs and symptoms of dry mouth. *Gerodontology*. 2010;27(2):129-133. doi:10.1111/j.1741-2358.2009.00293.x
- 80. Petersen P, Baez R, World Health Organization. *Oral Health Surveys: Basic Methods.* 5th ed. (World Health Organization, ed.).; 2013.
- 81. Coelho A, Amaro I, Caramelo F, et al. Dental caries, diabetes mellitus, metabolic control and diabetes duration: A systematic review and meta analysis. *Journal of Esthetic and Restorative Dentistry*. 2020;32(3):291-309.
- 82. Wang Y, Xing L, Yu H, Zhao L. Prevalence of dental caries in children and adolescents with type 1 diabetes: A systematic review and meta-analysis. *BMC Oral Health*. Published online 2019. doi:10.1186/s12903-019-0903-5

- 83. Novotna M, Podzimek S, Broukal Z, Lencova E, Duskova J. Periodontal Diseases and Dental Caries in Children with Type 1 Diabetes Mellitus. *Mediators Inflamm*. 2015;2015. doi:10.1155/2015/379626
- 84. Broadbent JM, Thomson WM. For debate: Problems with the DMF index pertinent to dental caries data analysis. Community Dent Oral Epidemiol. 2005;33(6):400-409. doi:10.1111/j.1600-0528.2005.00259.x
- 85. León-López M, Cabanillas-Balsera D, Martín-González J, et al. Does Diabetes Increase the Frequency of Root-Filled teeth: Systematic Review and Meta-Analysis of Observational Studies. *J Clin Exp Dent.* 2023;15(11):e945-e953. doi:10.4317/jced.61011
- 86. Ziukaite L, Slot DE, Van der Weijden FA. Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies. *J Clin Periodontol.* 2018;45(6):650-662. doi:10.1111/jcpe.12839
- 87. Tibúrcio-Machado CS, Michelon C, Zanatta FB, Gomes MS, Marin JA, Bier CA. The global prevalence of apical periodontitis: a systematic review and meta-analysis. *Int Endod J.* 2021;54(5):712-735. doi:10.1111/iej.13467
- 88. Segura-Egea JJ, Martín-González J, Castellanos-Cosano L. Endodontic medicine: Connections between apical periodontitis and systemic diseases. *Int Endod J.* 2015;48(10):933-951. doi:10.1111/iej.12507
- 89. Siqueira JF, Rôças IN. Present status and future directions in endodontic microbiology. *Endod Topics*. 2014;30(1):3-22. doi:10.1111/etp.12060
- 90. Siqueira JF, Rôças IN. Present status and future directions: Microbiology of endodontic infections. *Int Endod J.* 2022;55(S3):512-530. doi:10.1111/iej.13677
- 91. Chung YL, Lee JJ, Chien HH, Chang MC, Jeng JH. Interplay between diabetes mellitus and periodontal/pulpal-periapical diseases. *J Dent Sci.* 2024;19(3):1338-1347. doi:10.1016/j.jds.2024.03.021
- 92. Pimenta RMN, dos Reis Prado AH, de Castro Oliveira S, et al. Effects of diabetes mellitus on dental pulp: A systematic review of in vivo and in vitro studies. [published online ahead of print, 2022 Jun 3] Oral Dis. Published online 2022. doi:10.1111/odi.14267
- 93. Segura-Egea J, Castellanos-Cosano L, Machuca G, et al. Diabetes mellitus, periapical inflammation and endodontic treatment outcome. *Med Oral Patol Oral Cir Bucal.* 2012;17(2):356.
- 94. Dhamija R, Tewari S, Gill PS, Monga N, Mittal S, Duhan J. Association of Apical Periodontitis with Glycated Hemoglobin Levels and Systemic Inflammatory Markers in Patients with Type 2 Diabetes: A Cross-Sectional Study. *J Endod.* Published online 2024. doi:10.1016/j.joen.2024.11.008
- 95. Katz J, Rotstein I. Acute periapical abscesses and obese patients. . Am J Dent. 2024;37(4):197-200.
- 96. Paljević E, Brekalo Pršo I, Vidas Hrstić J, Božac E, Pezelj-Ribarić S, Peršić Bukmir R. Healing of apical periodontitis in type II diabetes mellitus patients: A prospective study. *Oral Dis.* 2024;30(5):3422-3430.
- 97. Budreikaitė K, Varoneckaitė M, Oleinikaitė D, Žilinskas J. Association between Apical Periodontitis and Root Canal Treatment in Patients with Type II Diabetes. A Systematic Review. Vol 24.; 2022.
- 98. Liu X, He G, Qiu Z, et al. Diabetes Mellitus Increases the Risk of Apical Periodontitis in Endodontically-Treated Teeth: A Meta-Analysis from 15 Studies. *J Endod*. 2023;49(12):1605-1616.
- 99. Bender IB, Seltzer S, Freedland J. The relationship of systemic diseases to endodontic failures and treatment procedures. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 1963;16(9):1102-1115.
- 100. Ruiz XF, Duran-Sindreu F, Shemesh H, et al. Development of Periapical Lesions in Endodontically Treated Teeth with and without Periodontal Involvement: A Retrospective Cohort Study. *J Endod.* 2017;43(8):1246–1249. doi:10.1016/j. joen.2017.03.037
- 101. Timmerman MF, Van Der Weijden GA. Bone level around endodontically treated teeth in periodontitis patients. *J Clin Periodontol.* 2006;33(9):620-625. doi:10.1111/j.1600-051X.2006.00958.x
- 102. Katsamakis S, Timmerman M, Van Der Velden U, De Cleen M, Van Der Weijden F. Patterns of bone loss around teeth restored with endodontic posts. *J Clin Periodontol*. 2009;36(11):940-949. doi:10.1111/j.1600-051X.2009.01465.x
- 103. Pinto KP, Serrão G, Ferreira CMA, Sassone LM, Da Silva Fidalgo TK, Silva EJNL. Association between apical periodontitis and chronic diseases: An umbrella review. *Iran Endod J.* 2023;18(3):134-144. doi:10.22037/iej.v18i3.42560
- 104. Corbet EF, Leung WK. Epidemiology of periodontitis in the Asia and Oceanic regions. *Periodontol 2000.* 2011;56:25-64.
- 105. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301(20):2129-2140.
- 106. Nascimento GG, Alves-Costa S, Romandini M. Burden of severe periodontitis and edentulism in 2021, with projections up to 2050: The Global Burden of Disease 2021 study. *J Periodontal Res.* Published online 2024. doi:10.1111/jre.13337
- 107. International Diabetes Federation. *IDF Diabetes Atlas.* 10th ed.; 2021. Accessed May 29, 2024. https://www.diabetesatlas.org
- 108. Cruz LR, Braga SF, Nadanovsky P, Santos APP Dos. Spin in dental publications: a scoping review. *Braz Oral Res.* 2024;38:e065. doi:10.1590/1807-3107bor-2024.vol38.0065
- 109. Committee on Publication Ethics. COPE Council. COPE Ethical Guidelines for Peer Reviewers English. .; 2017.
- 110. Arakawa N, Bader LR. Consensus development methods: Considerations for national and global frameworks and policy development. Research in Social and Administrative Pharmacy. 2022;18(1):2222-2229. doi:10.1016/j. sapharm.2021.06.024

- III. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical Guidelines Potential Benefits, Limitations, and Harms of Clinical Guidelines. www.bmj.com
- 112. Hunter J, Leach M, Braun L, Bensoussan A. An interpretive review of consensus statements on clinical guideline development and their application in the field of traditional and complementary medicine. *BMC Complement Altern Med.* 2017;17(1). doi:10.1186/s12906-017-1613-7
- 113. Simpson JK. Appeal to fear in health care: Appropriate or inappropriate? *Chiropr Man Therap.* 2017;25(1). doi:10.1186/s12998-017-0157-8
- 114. World Health Organization. Health Promotion Glossary of Terms 2021. Published online 2021.
- 115. Schmalz G, Ziebolz D. Changing the Focus to the Whole Patient instead of One Oral Disease: The Concept of Individualized Prevention. *Adv Prev Med.* 2020;2020:1-11. doi:10.1155/2020/6752342
- 116. Li S, Ning W, Wang W, et al. Oral Health-Related Quality of Life in Patients With Chronic Respiratory Diseases—Results of a Systematic Review. Front Med (Lausanne). 2022;8. doi:10.3389/fmed.2021.757739

"Het leven wordt vooruit geleefd, maar achteraf begrepen"

vrij naar Søren Kierkegaard

APPENDICES

Nederlandse samenvatting Contributing authors List of abbreviations About the author PhD portfolio Dankwoord



NEDERLANDSE SAMENVATTING

De levensverwachting van mensen stijgt wereldwijd. In Nederland was de gemiddelde levensverwachting in 1950 rond de 70 jaar, en dit is in de afgelopen decennia toegenomen tot 80 jaar. Er wordt verwacht dat deze levensverwachting na 2070 op ongeveer 90 jaar zal liggen. Deze toename gaat echter wel gepaard met een stijging in het aantal chronische aandoeningen. Naarmate mensen ouder worden, neemt de kans op het ontwikkelen van gezondheidsproblemen toe.

Diabetes mellitus is een chronische aandoening die wereldwijd steeds vaker voorkomt. Naar verwachting zullen in 2045 meer dan 780 miljoen mensen met diabetes op aarde leven. In Nederland hebben volgens het Diabetes Fonds 1,2 miljoen mensen diabetes, wat neerkomt op ongeveer 1 op de 14 personen. Het merendeel (90%) van deze groep heeft diabetes type II. Diabetes is een belangrijk gezondheidsprobleem dat invloed heeft op diverse aspecten van de gezondheid. Diabetes beïnvloedt niet alleen de bloedsuikerspiegel, maar vergroot ook het risico op hart- en vaatziekten. Daarnaast wordt diabetes steeds vaker in verband gebracht met de mondgezondheid. Met het steeds ouder worden en door de verleende tandheelkundige zorg behouden steeds meer mensen hun eigen tanden en kiezen, waardoor het belang van diabetes voor de mondgezondheid steeds groter wordt.

Dit proefschrift richt zich met name op de interactie tussen diabetes en mondgezondheid. De relatie tussen deze twee gezondheidsaspecten is de afgelopen jaren uitvoerig onderzocht en wordt vaak belicht in voorlichtingscampagnes, zowel voor (mond)zorgprofessionals als voor patiënten. Het onderzoek tussen mond- en systeemziekten is methodologisch een uitdaging, omdat beide complexe biologische sociale, en psychologische oorzaken hebben. Hoewel er bewijs is voor een associatie tussen diabetes en mondgezondheid, is het ook belangrijk om te bepalen hoe sterk dit verband werkelijk is. Bovendien is er tot nu toe onvoldoende aandacht besteed aan de klinische relevantie van deze relatie. Dit proefschrift heeft als doel om beter te begrijpen hoe sterk de associatie tussen diabetes en mondgezondheid is, de mogelijke causale verbanden te onderzoeken, en het bieden van praktische adviezen voor mondzorgprofessionals, onderzoekers en patiënten.

Diabetes mellitus

Diabetes mellitus is een stofwisselingsziekte waarbij het lichaam problemen heeft met de insulineproductie (type I) of de werking van insuline (type II). De oorzaak van diabetes type I is nog niet helemaal duidelijk. Het gaat om een auto-immuunziekte waarbij het immuunsysteem de cellen in de alvleesklier die insuline produceren, aanvalt. Het aantal mensen met diabetes type I neemt toe en de aandoening is tot nu toe niet te voorkomen. Diabetes type II komt ook steeds vaker voor, en het aantal mensen met deze ziekte groeit snel. De oorzaken van diabetes type II zijn beter bekend, waarbij leefstijl een belangrijke rol speelt. Overgewicht, vooral het hebben van te veel buikvet, is een belangrijke risicofactor. Daarnaast worden leeftijd, ongezonde voeding, onvoldoende lichaamsbeweging en roken gezien als risicofactoren voor het ontwikkelen van diabetes type II.

Mondgezondheid

Volgens de definitie van de wereld tandartsen organisatie (FDI) omvat mondgezondheid "de mogelijkheid om te spreken, lachen, ruiken, proeven, aan te raken, kauwen en het uitdrukken van emoties via de gezichtsuitdrukking met zelfvertrouwen en zonder pijn, ongemak en ziekten van de mond en kaak". Mondgezondheid weerspiegelt de fysiologische, psychologische, en sociale eigenschappen die essentieel zijn voor de kwaliteit van leven. Problemen in de mond, zoals het

verliezen van tanden en/of kiezen, kunnen ervoor zorgen dat mensen moeite krijgen met eten, praten of lachen. Dit kan ook psychische en sociale gevolgen hebben.

Twee belangrijke oorzaken van gebitsverlies zijn tandvleesontstekingen (gingivitis en parodontitis) en tandbederf (cariës). Wanneer gebitsverlies niet wordt behandeld, kan dit leiden tot volledige tandeloosheid (edentaat), waarbij een volledig kunstgebit ter vervanging van de ontbrekende gebitselementen de laatste optie is. Een kunstgebit is echter ook niet zonder problemen, waardoor preventie van gebitsverlies door tandvleesontstekingen en tandbederf beter is dan vervanging met een prothetische oplossing. Het behoud van eigen tanden en kiezen blijft dan ook het belangrijkste doel.

Cariës

Cariës, de tandheelkundige benaming voor tandbederf is een veelvoorkomende infectieziekte, waarbij het glazuur en het onderliggende tandbeen (dentine) van de tanden en kiezen wordt aangetast en er 'gaatjes' ontstaan. Bij cariës is er sprake van een complexe interactie tussen bacteriën, het voedingspatroon en het speeksel. Wereldwijd lijden naar schatting 2 miljard mensen aan cariës van de blijvende gebitselementen, en 514 miljoen kinderen hebben cariës in het melkgebit.

In de wetenschappelijke literatuur wordt gesuggereerd dat cariës vaker voorkomt bij diabeten als gevolg van veranderingen in de speekselproductie en verhoogde bloedsuikerspiegel in het speeksel. De meest gebruikte manier om de prevalentie van cariës in epidemiologische studies vast te leggen is de door de WHO aanbevolen DMF-index. Deze index bepaalt het aantal door cariës aangetaste (D; decayed), ontbrekende (M; missing) en gevulde (F; filled) tanden en kiezen (T; teeth) of tandoppervlakken (S; surfaces).

Wanneer cariës niet wordt behandeld of wanneer de behandeling niet succesvol is, kan caries dieper in de tand of kies doordringen tot aan de tandzenuw (pulpa). Dit kan leiden tot ontstekingen van de tandzenuw en uiteindelijk het afsterven ervan. In dat geval is een wortelkanaalbehandeling noodzakelijk, waarbij het afgestorven zenuwweefsel en bacteriën uit de wortelkanalen zo goed mogelijk verwijderd moeten worden en het wortelkanaal daarna zorgvuldig kan worden opgevuld. Een succesvolle wortelkanaalbehandeling kan de levensduur van de tand of kies aanzienlijk verlengen. Deze methode wordt daarom gezien als een effectieve manier om verlies van tanden en kiezen door vergevorderd tandbederf te voorkomen.

Parodontitis

Naar schatting heeft wereldwijd 90% van de mensen een vorm van tandvleesontsteking. Een oppervlakkige tandvleesontsteking wordt gingivitis genoemd, wat zijn oorzaak vindt in een overmaat aan tandplaque en de daarin aanwezige micro-organismen langs de tandvleesrand. Gingivitis is omkeerbaar met goede mondhygiënische zorg, eventueel aangevuld met een professionele gebitsreiniging. Wanneer de ontsteking zich echter uitbreidt naar de onderliggende weefsels, zoals de parodontale vezels die de tanden en kiezen ondersteunen en het kaakbot, spreekt men van parodontitis. Door parodontitis kan er uiteindelijk zoveel kaakbot worden afgebroken, wat niet meer herstelt, dat de tanden en kiezen los gaan staan en uiteindelijk verloren gaan.

Parodontitis is een belangrijk volksgezondheidsprobleem vanwege de hoge prevalentie. Het is de meest voorkomende chronische aandoening bij mensen en treft wereldwijd 20-50% van de wereldbevolking. In Nederland komt de ernstige vorm van parodontitis voor bij 10-15% van de volwassenen.

Door een combinatie van goede mondhygiënische zelfzorg en professionele behandeling kan de voortschrijding van parodontitis tot stilstand worden gebracht. De initiële fase

van de parodontale behandeling omvat het in kaart brengen van het niveau van zelfzorg, voorlichting, controle en begeleiding om de zelfzorg te optimaliseren, evenals adviezen over gezondheidsgedrag. Dit wordt in eerste instantie aangevuld met een professionele gebitsreiniging. Na evaluatie van de behandeling kan, indien nodig, een operatieve ingreep volgen, waarbij de gebitselementen met direct zicht grondig worden gereinigd en het niveau van het tandvlees en zo nodig ook de botcontour worden gecorrigeerd. Hierna volgt de nazorgfase waarin het gezond en stabiel houden van de parodontale conditie centraal staat.

Onderzoek naar twee ziekten

In onderzoek naar twee ziekten kan er sprake zijn van een oorzakelijk, ook wel causaal verband, waarbij de ene aandoening een oorzaak of gevolg van de andere is. Een direct oorzakelijk verband is bijvoorbeeld te zien bij het SARS-CoV-2-virus, dat de besmettelijke luchtwegaandoening COVID-19 veroorzaakt. In dit geval is er een duidelijke oorzaak-gevolgrelatie, waarbij besmetting met het virus (SARS-CoV-2) leidt tot het resultaat (COVID-19). Dit wordt een causaal verband genoemd, oftewel een oorzaak-gevolgrelatie. Het is echter door andere factoren die meespelen wel wisselend hoe ziek iemand daadwerkelijk wordt.

Bij roken en het ontwikkelen van longkanker is de situatie anders. Er is wel sprake van een oorzaak-gevolgrelatie, waarbij het gedrag (roken) kan leiden tot het resultaat (longkanker). Toch geldt dit niet voor iedereen want niet alle rokers krijgen longkanker en omgekeerd niet alle mensen met longkanker zijn (ex)rokers. In dit geval staan twee zaken met elkaar in verband, zonder dat de ene in alle gevallen direct en daadwerkelijk de andere veroorzaakt.

Ziekten kunnen dus gelijktijdig voorkomen zonder dat de ene ziekte de andere direct veroorzaakt. Er kan dan sprake zijn van een verhoogd risico, zoals in het voorbeeld van rokers die een verhoogd risico hebben op het krijgen van longkanker. Maar ook kunnen bijvoorbeeld andere factoren beide ziekten beïnvloeden, waardoor er geen directe oorzaak-gevolgrelatie is. Dit gevonden verband wordt een associatie genoemd. Een klassiek voorbeeld hiervan is de relatie tussen de verkoop van ijsjes en het aantal mensen dat verdrinkt. Als je dit verband onderzoekt lijkt het bijna lineair te zijn, namelijk als de verkoop van ijsjes toeneemt neemt ook het aantal verdrinkingen toe. Toch is het geen causaal verband maar speelt een derde factor 'mooi en zonnig weer' voor beide een rol. Kortom het verbieden van de verkoop van ijsjes zal geen effect hebben op het aantal verdrinkingen. Het onderscheid maken tussen causale verbanden en associaties is daarom belangrijk, vooral wanneer we proberen de sterkte van een relatie te begrijpen.

Als hulp om een mogelijk causaal verband in een associatie te ontdekken zijn de negen Bradford Hill-criteria voor causaliteit geïntroduceerd. Dit is een reeks van negen principes die vaak worden toegepast bij het vaststellen van een causaal verband tussen een veronderstelde oorzaak en een epidemiologisch waargenomen effect. Deze criteria helpen onderzoekers om de sterkte en de waarschijnlijkheid van een causaal verband te beoordelen (zie Tabel 1).

Tabel 1De Bradford Hill-criteria voor causaliteit

Criterium	Betekenis
Sterkte van het verband	Bij een sterk verband is een causale component waarschijnlijker dan bij een gering verband. De sterkte van het verband wordt bepaald door welk type de bestaande onderzoeken hebben. De onderzoeken die het hoogste niveau van de bewijspiramide vormen, staan daarbij voor de sterkste verbanden (bijv. gerandomiseerde klinische onderzoeken en systematische literatuuronderzoeken met meta-analyses). De resultaten van deze onderzoeken moeten een odds ratio of relatief risico vertonen van minimaal 2,0 of hoger om van betekenis te kunnen zijn. Alles tussen de 1 en 2 wordt beschouwd als zwak, terwijl >2 staat voor gering en >4 voor sterk. Noot: een kleine associatie betekent niet dat er geen causaal effect is, hoewel hoe groter de associatie, hoe waarschijnlijker het is dat er een
	causaal is.
Consistentie	In alle beschikbare onderzoeken wordt regelmatig een samenhang waargenomen
	Noot: Reproduceerbaarheid; consistente bevindingen door verschillende onderzoekers bij verschillende groepen versterken de aanname dat er een kans is op een effect.
Specificiteit	Een factor is specifiek van invloed op een bepaalde uitkomst of populatie. Hoe specifieker een verband is tussen een factor en een effect, hoe waarschijnlijker het is dat er sprake is van causaliteit.
	Noot: Als er een specifieke populatie met ziekte is zonder andere verklaring, dan is de kans groter dat er sprake is van een causaal verband.
Tijdelijkheid	De oorzaak moet vooraf zijn gegaan aan de uitkomst waarop hij vermoedelijk van invloed is (bijv. roken aan het ontstaan van longkanker). Uitkomsten gemeten op de langere termijn (longitudinaal onderzoek).
	Noot: Bij een vertraging is tussen de oorzaak en gevolg is nog steeds een causaal verband mogelijk.
Biologische gradiënt (Dosis- respons)	De uitkomst neemt lineair toe met de vergroting van de dosisblootstelling of op grond van een voorspellende functie van een substantieve theorie (bijv. hoe meer sigaretten iemand rookt, hoe groter diens kans is, longkanker te krijgen). Noot: De aanwezigheid van een factor kan voldoend zijn om een effect te veroorzaken (denk aan het gen voor borstkanker). Ook een omgekeerde verhouding kan bestaan, waarbij een grotere blootstelling leidt tot een lager

Plausibiliteit	Het waargenomen verband kan plausibel worden verklaard aan de hand van substantieve materie (bijv. of het biologisch mogelijk is). Noot: Ontbreken van kennis kan een beperking zijn.
Coherentie	Een conclusie ten aanzien van causaliteit mag niet fundamenteel in tegenspraak zijn met bestaande substantieve kennis. (Onderzoeken moeten elkaar niet tegenspreken.)
	Noot: Samenhang tussen epidemiologische bevindingen versterkt de aanname dat er causaal verband is. Het gebrek aan overig bewijs kan associaties niet teniet doen.
Experiment	Causaliteit is waarschijnlijker als het bewijs is gebaseerd op gerandomiseerde experimenten of op een systematisch literatuuronderzoek naar gerandomiseerde experimenten. Mogelijk zijn dergelijke gerandomiseerde klinische onderzoeken echter uit ethisch oogpunt niet mogelijk en zijn dus prospectieve observationele onderzoeken, zoals cohortonderzoeken, en niet experimentele onderzoeken het hoogst haalbare niveau van beschikbaar bewijs.
	Noot: Wees voorzichtig met verwijzen naar uitzonderingen, af.af en toe is het echter mogelijk om een beroep te doen op experimenteel bewijs.
Analogie	Voor analoge blootstellingen en uitkomsten is reeds een effect aangetoond (bijv. effecten die zijn aangetoond bij dieren, of een effect dat zich eerder bij mensen heeft voorgedaan, zoals de effecten van thalidomide op een foetus tijdens de zwangerschap).
	Noot: Overeenkomsten met andere gerelateerde of waargenomen associaties.

Bron: DE. Slot, GA. van der Weijden. Onderzoek, inzicht en advies. Hoe beoordeel je wetenschappelijk bewijs? 2021. Nederlands Tijdschrift voor Mondhygiëne.

Orginele bron: Lavigne SE. From Evidence to Causality: How Do We Determine Causality? [Online-college]. 2018. Beschikbaar via: www.dentalcare.com/en-us/professional-education/ce-courses/ce530

Sterke van een verband

Bij wetenschappelijk onderzoek worden uitkomstmaten gebruikt, oftewel meetresultaten en waarden waarop een ziekte of interventie wordt beoordeeld. In dit type onderzoek worden vaak termen gebruikt zoals het Relatief Risico (RR) en een Odds Ratio (OR) om de sterkte van een verband aan te geven. Een RR is de verhouding van het risico op een bepaalde uitkomst in de ene groep ten opzichte van het risico in een andere groep. Een OR vergelijkt de verhouding van de kansen dat een gebeurtenis zich voordoet in twee groepen.

In onderzoek kan op basis van een aantal criteria zoals die door de GRADE-working group zijn geïntroduceerd de sterkte van een verband van 2 ziekten worden geïnterpreteerd en gegradeerd. Voor het gemak zou je dit kunnen vergelijken met de indeling van sterktes van alcoholische dranken. Hoe sterker het verband, hoe groter het effect. Hoe hoger het cijfer, hoe sterker het effect. In tabel 2 staat een overzicht en toelichting van de schaal.

Tabel 2Toelichting op mate van effect van RR en OR met alcohol concentraties in dranken als metafoor

Mate van Effect	Alcohol voorbeeld	Toelichting
Geen Effect	Geen alcohol –	Er zit geen alcohol in, en je merkt geen effect.
	Bijv. Alcohol vrij bier	Noot: Op dezelfde manier betekent een RR of OR van 1 dat er geen verband is tussen de onderzochte factoren. Alles blijft zoals het is.
Klein Effect	Licht alcoholisch – Bijv. Bier	Het alcoholpercentage is laag, en het effect is mild. Je merkt een kleine verandering. Noot: Dit kun je vergelijken met een klein verband in een onderzoek: het effect is aanwezig, maar klein (RR >1.22 of OR >1.68).
Gemiddeld Effect	Gemiddeld alcoholisch – Bijv. Wijn	Met een hoger alcoholpercentage merk je het effect duidelijker. Noot: Dit staat voor een middelmatig sterk verband in een onderzoek (RR >1.86 of OR >3.47).
Sterk Effect	Sterk alcoholisch – Bijv. Whisky	Het hoge alcoholpercentage zorgt voor een krachtig effect dat je niet kunt negeren. Noot: Dit is vergelijkbaar met een sterk verband en een groot effect in een onderzoek (RR > 3.00 of OR > 6.71).

Een wetenschappelijk verband kan worden aangevuld met een statistische analyses op basis waarvan de significantie van resultaten kan worden bepaald. Wanneer resultaten als significant worden beschouwd, betekent dit dat de kans klein is dat de bevindingen toevallig zijn. Echter, een statistisch significant effect betekent niet altijd dat het ook klinisch relevant hoeft te zijn. Neem bijvoorbeeld, een nieuw medicijn dat wordt getest om mensen met overgewicht te helpen afvallen. Er wordt een daling van gewicht waargenomen, en de resultaten blijken statistisch significant te zijn, wat aangeeft dat het medicijn in veel gevallen een positief effect heeft. Maar stel dat de daling in gewicht slechts 2-4 kilo bedraagt. Dit is mogelijk onvoldoende effect voor mensen met veel overgewicht, aangezien zij veel meer moeten afvallen om gezondheidsvoordelen te behalen. Met andere woorden, hoewel het resultaat statistisch significant is, kan het in de praktijk onvoldoende impact hebben op de gezondheid van de patiënt. Naast significantie biedt de gevonden breedte van het bereik waarin de resultaten vallen meer inzicht in de precisie van de meting. Een breder bereik wijst op een lagere precisie, omdat de metingen meer variëren en minder consistent zijn. Dit betekent dat de nauwkeurigheid van de resultaten afneemt. Bijvoorbeeld, een weersvoorspelling die aangeeft dat de temperatuur tussen de 10-12 graden ligt, is preciezer dan wanneer de voorspelling tussen de 8-14 graden ligt. Hoe smaller het bereik, hoe consistenter en preciezer de meting is, wat zorgt voor een meer betrouwbare voorspelling.

Bidirectionele relatie diabetes en parodontitis

In de literatuur wordt parodontitis in verband gebracht met andere aandoeningen, waaronder diabetes. Er wordt gesuggereerd dat parodontitis niet alleen invloed heeft op diabetes, maar ook omgekeerd dat diabetes ook een effect heeft op parodontitis. Dit wordt een bidirectioneel (twee richtingen op) verband genoemd. Zo wordt er aangenomen dat parodontitis mogelijk niet alleen het risico op en de instelling van diabetes vergroot, maar dat diabetes ook van invloed is op het ontwikkelen en de ernst van parodontitis.

In hoofdstuk 4 van dit proefschrift wordt de parodontale conditie van diabetes patiënten vergeleken met niet-diabeten op basis van een samenvatting van de huidige beschikbare wetenschappelijke literatuur. De resultaten tonen aan dat patiënten met diabetes een significant slechtere parodontale conditie hebben in vergelijking met niet-diabeten. Hoewel er statistisch significante verschillen worden gevonden, variëren deze in klinische relevantie, grootte en precisie. Dit betekent in de praktijk dat het risico en de ernst van parodontitis verschilt tussen diabeten en niet-diabeten, en dat dit niet bij voorbaat slechter is voor alle patiënten met diabetes. Dit nuanceert de algemene bewering uit de literatuur dat diabetes invloed heeft op de ontwikkeling en ernst van parodontitis.

Andersom kan parodontitis mogelijk de bloedsuikerspiegel negatief beïnvloeden. In hoofdstuk 3 van dit proefschrift blijkt echter dat dit verband minder sterk is dan wel wordt gesuggereerd. Uit de resultaten blijkt dat factoren zoals geslacht, de ernst van parodontitis, roken en het continent van herkomst van de beschreven populatie een rol spelen in deze relatie. In 57% van de geanalyseerde associaties werd een relatief klein risico vastgesteld, terwijl het risico in 29% zelfs als verwaarloosbaar werd beoordeeld. Bovendien werd op basis van de Bradford Hill-criteria geen bewijs gevonden voor een causaal verband tussen parodontitis en veranderingen in de bloedsuikerspiegel.

In de wetenschappelijke literatuur wordt diabetes ook in verband gebracht met een twee tot vier keer hoger risico op het ontwikkelingen van hart- en vaatziekten. Bovendien wordt er gesuggereerd dat hart- en vaatziekten vaker voorkomen bij mensen met ernstige parodontitis. **Hoofdstuk 2** van dit proefschrift onderzoekt hoe sterk parodontitis samenhangt met hart- en vaatziekten. Dit onderzoek toont aan dat de grootte van associatie tussen parodontitis en hart- en vaatziekten klein is. Ook in dit geval spelen factoren zoals geslacht, leeftijd, de ernst van parodontitis en het continent van herkomst van de onderzochte populatie een rol in de relatie. Er werd geen duidelijke aanwijzing voor causaliteit gevonden op basis van de Bradford Hill-criteria.

Het effect van een professionele gebitsreiniging in combinatie met het optimaliseren van de zelfzorg voor het tot stilstand brengen van parodontitis werd onderzocht in **hoofdstuk 5**. Hieruit blijkt dat er geen verschil is tussen diabetes en niet-diabetes parodontitis patiënten op behandeluitkomsten die gebruikt worden voor het succes van parodontale therapie. Diabetes patiënten met parodontitis die een professionele parodontale behandeling ondergaan kunnen dus net zo effectief behandeld worden als patiënten zonder diabetes.

Relatie diabetes en caries

Hoofdstuk 6 evalueert de prevalentie van cariës op basis van de DMF score tussen mensen met diabetes en mensen zonder diabetes. Uit dit onderzoek blijkt dat diabeten significant hogere cariës scores laten zien. Het verschil tussen diabeten en niet-diabeten is 3.01 voor de DMFT score (tandniveau) en 10.30 voor de DMFS score (tandoppervlak niveau). De grootte van dit effect kan op basis van de WHO-criteria voor mondgezondheid wordt echter als klein beoordeeld. Deze uitkomst is onafhankelijk van het type diabetes (type I of type II).

Een wortelkanaalbehandeling kan worden gezien als een indicatie voor diepe cariës

die tot aan de tandzenuw was doorgedrongen. Het verkrijgen van inzicht in het aantal wortelkanaalbehandelingen bij patiënten met diabetes in vergelijking met patiënten zonder diabetes kan helpen om de actieve rol van diabetes als oorzakelijke factor voor ernstig en uitgebreid tandbederf beter te begrijpen. Het aantal wortelkanaalbehandelingen tussen welen niet-diabeten werd in **hoofdstuk 7** onderzocht. Er werden geen significante verschillen gevonden in het aantal endodontisch behandelde tanden of kiezen. Dit was 6,9% voor de diabetespatiënten versus 7,3% bij de niet-diabeten. Dit suggereert dat diabetes geen risicofactor is voor de mate van tandbederf die leidt tot een ontsteking van de tandzenuw waarvoor een wortelkanaalbehandeling werd uitgevoerd.

Relatie diabetes en tandverlies

Tandverlies is een van de belangrijkste gevolgen van parodontitis en cariës. In **hoofdstuk 8** wordt een significant verhoogd risico op tandverlies gevonden voor diabeten in vergelijking met niet-diabeten. De grootte van dit risico, weergegeven als Relatief Risico (RR), blijkt 1.63. Deze uitkomst kan op basis van de daarvoor op van toepassing zijnde criteria als klein worden beschouwd. Het risico is echter hoger voor patiënten met slecht gecontroleerde diabeteswaarden. Bovendien blijkt het risico groter in onderzochte populaties uit landen in Azië en Zuid-Amerika dan in Europa en Noord-Amerika.

De ultieme graadmeter voor tandverlies is tandenloosheid. De prevalentie van tandeloosheid werd onderzocht in **hoofdstuk 9**. Dit blijkt op basis van een samenvatting van de literatuur 14% voor mensen met diabetes ten opzichte van 7% voor niet-diabeten. Hoewel de Odds Ratio (OR = 2.39) met matige zekerheid aangeeft dat het risico op tandeloosheid bij diabetes patiënten in vergelijking met niet-diabeten significant is, wordt op basis van de daarvoor op van toepassing zijnde criteria dit als een klein effect beoordeeld.

CONCLUSIE

Dit proefschrift benadrukt de complexiteit van de relatie tussen diabetes en mondgezondheid, evenals de interpretatie ervan. Hoewel er een verband bestaat, dat soms significant is, blijkt de sterkte van deze associatie vaak minder overtuigend dan wat door wetenschappelijke verenigingen en instanties wordt gesuggereerd. Bovendien is de klinische relevantie in veel gevallen beperkt. Binnen de tandheelkunde blijft diabetes een factor in de context van mondgezondheid. Echter, bij gebrek aan een duidelijk onderbouwde causale relatie, dient de tandheelkundige aandacht primair gericht te zijn op het voorkomen van mondaandoeningen door het bevorderen van goede mondhygiënische zelfzorg en het uitvoeren van regelmatige periodieke mondonderzoeken.

PRAKTISCHE HANDVATEN

Aanbevelingen voor patienten

Optimale zelfzorg is het fundament voor het verkrijgen en behouden van een gezonde mond. Het 'basisadvies mondhygiëne' van het Ivoren Kruis is de tanden en kiezen 2x per dag 2 minuten te poetsen met de juiste fluoridetandpasta, afhankelijk van de leeftijd. Gebruik van aanvullende mondhygiënische hulpmiddelen wordt aanbevolen indien geïndiceerd. Het regelmatig bezoeken van de tandarts en mondhygiënist is belangrijk om vroegtijdig problemen op te sporen en te behandelen.

Aanbevelingen voor mondzorgprofessionals

Mondzorg professionals kunnen patiënten informeren over het verband tussen mondgezondheid en diabetes, maar moeten de sterkte van dit verband niet overschatten en zeker niet als oorzaak aangeven. Diabetici met cariës en/of parodontitis moeten worden behandeld volgens de heersende behandelstandaard, gericht op het behoud van het gebit. Preventie van mondziekten zoals cariës en/of parodontitis moet de tandheelkundige focus zijn wat begint met optimale mondhygiënische zelfzorg.

Aanbevelingen voor onderzoekers

In onderzoeken moet statistische significantie altijd worden aangevuld met effectgrootten en bijbehorende betrouwbaarheidsintervallen, of worden gepresenteerd aan de hand van de sterkte van de associatie of correlatie. Daarbij is het van belang dat er voldoende aandacht wordt gegeven worden aan de klinische relevantie van de bevindingen en de interpretatie ervan. Mogelijke causaliteit van associaties kan worden geëvalueerd aan de hand van de negen Bradford Hill-criteria.



CONTRIBUTING AUTHORS

Chapter 2

The association of periodontitis with cardiovascular disease parameters - a synthesis of systematic reviews.

M.G.P. Schoenmakers, L.P.M. Weijdijk, E.J.S. Willems, G.A. van der Weijden, D.E. Slot

Authors contributions:

MGPS: contributed to design, search and selection, analysis and interpretation, and drafted the manuscript.

LPMW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

EJSW: contributed to search and selection and critically revised the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

Chapter 3

The association of periodontitis with diabetes mellitus - a synthesis of systematic reviews. E.J.S. Willems, L.P.M. Weijdijk, M.G.P. Schoenmakers, G.A. van der Weijden, D.E. Slot

Authors contributions:

EJSW: contributed to conception and design, search and selection, analysis and interpretation, and drafted the manuscript.

LPMW: contributed to conception and design, search and selection, analysis and interpretation, and drafted the manuscript.

MGPS: contributed to search and selection and critically revised the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

Chapter 4

What is the clinical periodontal condition of patients with diabetes mellitus as compared to those without? - a synthesis of systematic reviews -

L.P.M. Weijdijk, G.A. van der Weijden, S. Asadi, D.E. Slot

Authors contributions:

LPMW: contributed to conception and design, search and selection, analysis and interpretation, and drafted the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

SA: contributed to search and selection and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

Chapter 5

The effect of diabetes on outcomes of non-surgical periodontal therapy: a systematic review with a meta-analysis and trial sequential analysis

L.P.M. Weijdijk, T.M.J.A. Thomassen, N.C. de Keyzer, E.E.J. Mayer, C. Valkenburg, G.A. van der Weijden, D.E. Slot

Authors contributions:

LPMW: contributed to conception and design, search and selection, analysis and interpretation, and drafted the manuscript.

TMJAT: contributed to selection, analysis and interpretation and critically revised the manuscript.

NCK: contributed to contributed to selection, analysis and interpretation of the data.

EEJM: contributed to analysis and critically revised the manuscript.

CV: contributed to analysis and critically revised the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

Chapter 6

DMF scores in patients with diabetes: a systematic review and meta-analysis of observational studies

L.P.M. Weijdijk, G.A. Van der Weijden, D.E. Slot

Authors contributions:

LPMW: contributed to the design, search and selection, analysis and interpretation, and drafted the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

Chapter 7

Comparing endodontic treatment prevalence in diabetes mellitus and non-diabetic periodontitis patients: a retrospective case-control investigation

L.P.M. Weijdijk, D.E. Slot, M. el Kadi, G.A. Van der Weijden

Authors contributions:

LPMW: contributed to conception and design, collected the data, analyzed the data, and drafted the manuscript.

GAW: contributed to conception and design, analyzed the data, and critically revised the manuscript.

MK: collected the data and analyzed the data and drafted the initial manuscript.

DES: contributed to conception and design, analyzed the data, and critically revised the manuscript.

Chapter 8

The risk of tooth loss in patients with diabetes: a systematic review and meta-analysis L.P.M. Weijdijk, L. Žiūkaitė, G.A. Van der Weijden, E. Bakker, D.E. Slot

Author contributions:

LPMW: contributed to design, search and selection, analysis and interpretation, and drafted the manuscript.

LZ: contributed to design, analysis and interpretation, and critically revised the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

EWPB: contributed to analysis and interpretation and critically revised the manuscript.

DES: contributed to conception and design, search and selection, analysis and interpretation, and critically revised the manuscript.

Chapter 9

Edentulism among diabetic patients compared to non-diabetic controls - a systematic review and meta-analysis

L. Žiūkaitė, L.P.M. Weijdijk, J. Tang, D.E. Slot, G.A. van der Weijden

Author contributions:

LZ: contributed to search and selection, analysis and interpretation, and critically drafted the manuscript.

LPMW: contributed to the design, search and selection, quality assessment, analysis and interpretation of data, and critically revised the manuscript.

JT: contributed to the design, analysis and interpretation of data and helped draft the manuscript.

DES: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.

GAW: contributed to conception and design, analysis and interpretation, and critically revised the manuscript.



LIST OF ABBREVIATIONS

AAP American Academy of Periodontology

ABI Ankle brachial index

ACTA Academic Centre for Dentistry Amsterdam

ACS acute coronary syndrome

ACVD atherosclerotic cardiovascular disease AGEs Advanced Glycation End Products

AF atrial fibrillation
AL attachment level

AMSTAR A MeaSurement Tool to Assess systematic Reviews

AP apical periodontitis
BMI Body mass index
BOP bleeding on probing
BS bleeding score
CA clinically assessed

CAC carotid artery calcification, coronary artery calcium

CAD Carotid atherosclerosis
CAL clinical attachment level/loss

cc case-control study

CBM Chinese BioMedical Literature Database
CDHA Canadian Dental Hygienist Association

CEJ cement-enamel joint
CHD coronary heart disease
Cl confidence interval

c-IMT Carotid intima media thickness

CNKI China National Knowledge Infrastructure

CS cross-sectional study $\mathbb{C}\mathbb{V}$ Cees Valkenburg CVD cardiovascular disease CVD/CVE cardiovascular diseases CVE cardiovascular event DA descriptive analysis DES Dagmar Else Slot DFS decayed-filled-surfaces difference of means DiffM

DM diabetes mellitus
DM I diabetes mellitus type I
DM II diabetes mellitus type II

DM I/II diabetes mellitus type I and II grouped or merged

DM I+II diabetes mellitus type I and II separate
DM B diabetes mellitus type I or II or both

DM + diabetics
DM - non-diabetics

DMF decayed-missed-filled

DMFS decayed-missed-filled-surfaces
DMFT decayed-missed-filled-teeth

DMR dental/medical record

E edentulousness
EB Eric Bakker

EBM Evidence Based Medicine

EEJM Julia Mayer

EFCD European Federation of Conservative Dentistry

EFP European Federation of Periodontology

EJSW Eveline Willems
EWPB Eric Bakker

FEM fixed effect model
FMD Flow mediated dilatation
FPG fasting plasma glucose

GAW Godefridus August van der Weijden

GBD Global Burden of Disease
GBI gingival bleeding index
GDM gestational diabetes mellitus

GI gingival index

GRADE Grading of Recommendations Assessment, Development, and

Evaluation

HAS Helsinki Aging Study
HbA1c glycated haemoglobin

HCHS/SOL Hispanic Community Health Study/Study of Latinos

HeterogHeterogeneousHomogHomogeneousHRhazard ratioHThypertension

ICDAS international caries detection and assessment system

iddm insulin dependent diabetes mellitus IDF International Diabetes Federation

IHD ischemic heart disease

² Higgins test for heterogeneity

JBI Joanna Briggs Institute

JT Jennifer Tang local anesthesia

LILACS Latin American and Caribbean Health Sciences

LPMW Lotte Phinè Marie Weijdijk

LZ Laura Žiūkaitė m months MA Meta-analysis

MetSMetabolic SyndromeMGPSMax SchoenmakersMImyocardial infarctionmimanual instrumentationMKMohammed el Kadi

MOOSE Meta-analyses Of Observational Studies in Epidemiology

MR meta review

N number of participants

NA not applicable

NCDs noncommunicable diseases

NCK Nikita de Kezer

NDM people without diabetes mellitus
NDF Nederlandse Diabetes Federatie
NHG Nederlands Huisarts Genootschap

NHMRC National Health and Medical Research Council niddm non-insulin-dependent diabetes mellitus

non-DM people without diabetes mellitus non-PerioD people without periodontal disease

NOS Newcastle-Ottawa Scale

NR not reported

NSPT non-surgical periodontal therapy
OGTT oral glucose tolerance test
OHRQoL oral health-related quality of life

OR odds ratio

ORCA European Organization for Caries Research

PAD peripheral artery disease
PAL probing attachment level
PD professionally diagnoses

PECOS population, exposure, comparison, outcomes and study

PESA periodontal epithelial surface area

PerioD periodontitis Pl plaque index

PICOS population, intervention, comparison, outcomes and study

PISA periodontal inflamed surface area
PMT Periodontal maintenance therapy

PPD periodontal pocket depth

PrDM Previous known diabetes mellitus

Prof D Professionally diagnosed

PROSPERO Prospective Register of Systematic Reviews

PRISMA-P Preferred Reporting Items for Systematic Review and Meta-

Analysis Protocols

PVD peripheral vascular disease

QoL Quality of Life Questionnaire

Q* Cochran's Q test for heterogeneity

RAL Relative Attachment Level randomized controlled trial

REC gingival recession
REM random effect model
RIS required information size

Ri*** DerSimonian and Laird Q test for heterogeneity

RoB Risk of Bias

ROBINS-E Risk of Bias in Non-randomized Studies - of Exposures
ROBINS-I Risk of Bias in Non-randomized Studies - of Interventions

RR relative risk

SA Shabnam Asadi

ScDM Screening detected diabetes mellitus

SD standard deviation Self-R Self-reported

SHIP Study of Health in Pomerania

Sig(n) significant

SMD standardized mean difference

SR systematic review
SRR summary relative risk
SRP scaling rootplaning

TIA Transient ischemic attack

TMJAT Tim Thomassen

TSA Trial Sequential Analysis

TSMB trial sequential monitoring boundaries

T- Missing teeth
T+ Present teeth
T1DM Type 1 diabetes
T2DM Type 2 diabetes

Type I and/or II

Distinction is made between diabetes type I and II

Type I/II

No distinction is made between type of diabetes

SPC supportive periodontal care

SR systematic review SR* self-reported

SRR summary relative risk
UPS Université Paul Sabatier
usi ultrasonic instrumentation
UVA University of Amsterdam
VPI visible plaque index

w weeks

WHO World Health Organization
WHF World Heart Federation
WMD Weighted mean difference

WONCA National Colleges, Academies and Academic Associations of

General Practitioners/Family Physicians

X2** Chi-square test for heterogeneity

? not reported/unknown◊ researchers' calculation•, data provided by author,

ABOUT THE AUTHOR



Lotte Weijdijk werd op 14 september 1995 geboren in Enschede en groeide op in een warm gezin samen met haar ouders en jongere broer Wessel. In 2012 behaalde ze haar middelbareschooldiploma aan het Bonhoeffer College, waarna ze naar Utrecht verhuisde om Mondzorgkunde te gaan studeren aan de Hogeschool Utrecht. Ze rondde deze opleiding in 2016 af. Later volgde ze de TMS-cursus en werd ze geregistreerd in het BIG-register. Haar interesse in wetenschappelijk onderzoek leidde Lotte naar de master Evidence-Based Practice in Health Care aan de Faculteit Geneeskunde van de Universiteit van Amsterdam. Ze voltooide deze opleiding in 2020 en behaalde de titel van klinisch epidemioloog. Tijdens haar afstudeeronderzoek kwam ze in contact met Fridus van der Weijden en Dagmar Else Slot. Haar masterthesis werd destijds gepubliceerd en is opgenomen als hoofdstuk 8 van dit proefschrift.

Vanaf haar afstuderen als mondhygiënist tot 2025 werkte Lotte in diverse praktijken, waaronder geruime tijd bij het Amsterdam UMC en een algemene tandartspraktijk in Utrecht. In deze jaren ontwikkelde ze een passie voor de parodontologie en tandheelkundige ziekenhuiszorg, met een bijzondere interesse in de relatie tussen mondgezondheid en systemische aandoeningen. Dit versterkte haar nieuwsgierigheid naar de vertaalslag van wetenschappelijke uitkomsten naar de praktijk en hoe zorgprofessionals deze inzichten kunnen integreren in de dagelijkse patiëntenzorg.

Voortbouwend op haar passie voor onderzoek en interesse in de zogenoemde "systemic link" begon ze in 2021 aan een promotietraject aan het Academisch Centrum Tandheelkunde Amsterdam (ACTA). Hiervoor werden begeleiders bereid gevonden vanuit de sectie parodontologie en sectie mondziekten, kaak- en aangezichtschirurgie. Ze combineerde haar promotieonderzoek, dat ze grotendeels in haar eigen tijd uitvoerde, met het werk als mondhygiënist, waardoor haar expertise in evidence-based gezondheidszorg verder werd versterkt.

Haar onderzoek kreeg brede erkenning en ondersteuning met name het hoofdstuk 6. In 2021 ontving ze een beurs van The National Center for Dental Hygiene Research & Practice, gefinancierd door Crest en Oral-B. In 2022 werd haar werk bekroond met de VMTI-publicatieprijs. In 2024 ontving ze een reisbeurs van het Genootschap ter Bevordering van de Natuur-, Genees- en Heelkunde om haar onderzoek te presenteren op het IADR-congres in New Orleans. Daarnaast werd ze dat jaar de eerste ontvanger van de NVM-publicatieprijs.

Naast haar onderzoek en klinische werkzaamheden is Lotte actief lid van de Nederlandse Vereniging voor Mondhygiënisten (NVM). Daarnaast behaalde ze de Basis Kwalificatie Onderwijs (BKO) aan de Vrije Universiteit Amsterdam, waardoor ze bevoegd is om les te geven in het hoger onderwijs. Bovendien is ze geregistreerd in het BROK-register (Basisregistratie Mens gebonden Onderzoek), waarmee ze haar bekwaamheid aantoont in het uitvoeren van medisch wetenschappelijk onderzoek bij mensen.

Sinds 2025 heeft Lotte haar loopbaan in de mondzorg verruild voor een bredere rol binnen de medische sector. Recent is ze gestart als adviseur bij het Kennisinstituut van de Federatie Medisch Specialisten. In deze functie zet ze haar expertise in klinische epidemiologie in om medische professionals te ondersteunen bij de ontwikkeling en implementatie van kwaliteitsinstrumenten en geïntegreerd kwaliteitsbeleid.

PHD PORTFOLIO

PhD candidate: Lotte Phinè Marie Weijdijk

Profession: Registered Dental Hygienist

Clinical Epidemiologist

Graduate school: Dentistry

Position: External promovendus

PhD period: March 2021 – May 2025

Promotores: prof. dr. D.E. Slot

prof. dr. J. de Lange

Co-promotores: prof. dr. G.A. van der Weijden

Identifiers

BIG registration number: 49930232579

KRM registration number: 2000357

ORCID: 0000-0001-7910-9778

Web of Science Researcher ID: AAB-2137-2022

BROK registration number: 36838

PhD training

	subtotal	91 EC
Master thesis	2020	24 EC
Health Care System Evaluation	2020	7 EC
Health Economics	2020	6 EC
Clinimetrics	2020	8 EC
Biostatistics & Advanced Epidemiolgy	2019	9 EC
Systematic Reviews and Clinical Guidelines	2019	6 EC
Biostatistics	2019	9 EC
Epidemiology and Evidence Based Practice: De	signs 2019	12 EC
Epidemiology and Evidence Based Practice: Co	oncepts 2018	10 EC
University of Amsterdam (Academic Medical	Centre)	
General courses	Year	ECTS

ACTA Graduate school of Dentistry

Scientific integrity	2021	2.0 EC
Writing and presenting in English	2023	4.0 EC
Guidance and training (mentoring, supervising)	Continuously	
Scientific afternoon meetings	Continuously	
Perio workshop meetings	Continuously	
Supervision of students master Dentistry	Continuously	
	subtotal	6 EC
Specific courses		
BROK course - NFU	2023	1.5 EC
Writing a Data Management Plan – VU	2023	1.0 EC
Basiskwalificatie onderwijs VU Learn! Academy	2024	5.4 EC
	subtotal	7.9 EC
National conferences		
NVM-ICO Zuilen	2018 - 2024	
NVM regiobijeenkomst	2018	0.1 EC
VPM-congres; mondgezondheid doe je samen	2019	0.2 EC
VvE symposium; Epidemiology across borders	2019	0.2 EC
NVvP webinar; nieuwe richtlijn parodontologie	2020	0.1 EC
NVM webinar; leidraad mondzorg cororna	2020	0.1 EC
NTVT webinar; Patiënt met corona aan de telefoon, wat nu?	2020	0.1 EC
FDI Oral Health campus; the road to achieving and maintaining periodontal health: Contemporary step-by-step periodontal treatment & care	2020	0.1 EC
Fresh tandartsen webinar; jong geleerd is out geprofiteerd!	2021	0.1 EC
Toezichthoudend medewerker stralingsbescherming THK	2021	0.5 EC
Tepe webinar; "Smoking Cessation in Dental Practice "Do you Mind if I Vape"?Well do we?"	2021	0.1 EC
Dentiva webinar; De praktische vertaalslag van de nieuwe	2021	0.1 EC
richtlijnen Mondzorg voor Jeugdigen		
NVM webinar vakgroepbijeenkomst IZ, MO	2021	0.1 EC
Dentiva webinar; praktische vertaalslag van de nieuwe tarieven voor de mondzorg 2022	2021	0.1 EC

	Total	117 EC
	subtotal	2.0 EC
Dutch Dental Science Days, Lunteren (oral presentation)	2024	1.0 EC
Perio workshop, ACTA (oral presentation)	2024	1.0 EC
Dutch Dental Science Days, Lunteren (poster presentation)	2023	0.5 EC
Presentations national Quality Practice, ACTA (poster presentation)	2023	0.5 EC
	subtotal	1.5 EC
ISDH, Seoul, South Korea (oral presentation)	2024	1.0 EC
IADR, New Orleans, USA (poster presentation)	2024	0.5 EC
Presentations international		
	subtotal	4.0 EC
ISDH, Seoul, South Korea	2024	1.5 EC
IADR, New Orleans, USA	2024	2.0 EC
Design & Conduct of Clinical Trials Interactive Workshop – Task Force Group, New Orleans, USA	2024	0.5 EC
International conferences		
	subtotal	4.6 EC
Dutch Dental Science Days	2024	1.0 EC
Basic Life Support	2024	0.1 EC
Dutch Dental Science Days	2023	0.5 EC
QP; up to date voor mondygiënisten	2023	0.2 EC
Symposium ACTA; Burna is Litouws voor mond!	2023	0.2 EC
Symposium ACTA; Preventie en mondzorg, de mens centraal	2023	0.2 EC
NVVP lustrumcongres	2022	0.5 EC

Reviewer for International scientic journal

International Journal of Dental Hygiene	Continuously
GRANTS and prices	
GRANTS and prices	
National center for Dental Hygiene Research & Practice	2021
VMTI Publication Award	2023
Travel grant Genootschap ter bevordering Natuur-,	2024
Genees- en Heelkunde	
NVM Publication Award	2024

DANKWOORD

Bij het afronden van dit proefschrift wil ik graag mijn dank uitspreken aan een aantal personen die mij door dik én dun hebben gesteund.

De leden van de promotiecommissie en oppositie wil ik hartelijk danken voor het lezen en beoordelen van het manuscript en voor de tijd die zij aan mijn promotie hebben besteed. Zonder hun zegen, geen ceremonie. Bedankt prof. dr. C. Lucas, prof. dr. M. Timmerman, prof. dr. B. Loos, prof. dr. F. Rozema, dr. E van der Sluijs, dr. R. Thomas en dr. M.M. Danser.

Niets dan lof voor mijn promotor, **prof. dr. Slot.** Beste Dagmar, je was mijn steun en toeverlaat—altijd beschikbaar, niet alleen voor vragen over mijn onderzoek, maar ook voor advies en steun op persoonlijk vlak. Op momenten van twijfel gaf je me niet alleen het vertrouwen om door te gaan, maar ook de rust en ruimte om mijn eigen koers te bepalen. Jouw geduld en scherpe inzichten hebben niet alleen bijgedragen aan dit proefschrift, maar ze hebben mij ook verder gevormd als persoon. Jouw mensenkennis is indrukwekkend, en inhoudelijk ben je minstens zo sterk. En ja, je eerlijkheid... die was soms confronterend. Geen omwegen of verzachtende woorden—gewoon recht door zee. Was dat altijd makkelijk? Niet altijd, maar ik ben je dankbaar voor deze oprechtheid. Dank je wel voor alles wat je mij hebt geleerd, voor je onmiskenbare steun en voor je begeleiding die mij geholpen heeft om mijn eigen weg te vinden.

Prof. dr. van der Weijden, beste Fridus. Tijdens dit traject ben jij enorm waardevol geweest. Jouw scherpe en verfrissende blik heeft mij geholpen om mijn werk naar een hoger niveau te tillen. Ik ben je erg dankbaar voor de aandacht en nauwkeurigheid waarmee je mijn stukken hebt nagekeken en voor de kritische vragen die mij uitdaagden om verder te denken. Dankzij jou heb ik niet alleen geleerd om oog te hebben voor details, maar ook om het grotere geheel te zien en mijn onderzoek te plaatsen binnen de bredere context van ons vakgebied. Daarnaast heb ik genoten van onze gesprekken wanneer het even niet over onderzoek ging, zoals de momenten in New Orleans. Dit heeft bijgedragen aan een gevoel van verbondenheid en inspiratie. Ik waardeer je toewijding, je kritische blik en de fijne manier waarop we hebben samengewerkt. Dankjewel Fridus.

Lieve Dagmar en Fridus, samen hebben jullie een unieke onderzoeksgroep opgebouwd, waar samenwerking, humor en enthousiasme de basis vormen. Ik ben dankbaar dat ik daar deel van mocht uitmaken. Het was én is een eer om met jullie samen te werken.

Prof. dr. de Lange, beste Jan. Bedankt voor het vertrouwen om dit promotietraject met mij aan te gaan. Ik waardeer de ruimte die ik heb gekregen om dit proefschrift te ontwikkelen. Deze vrijheid heeft mij in staat gesteld om mijn eigen ideeën te verkennen, wat heeft geleid tot een resultaat waar ik trots op ben. Jij hebt mij geholpen om zelfstandig te denken en mijn onderzoek op mijn eigen manier vorm te geven. Ik waardeer de kans die ik heb gekregen om dit traject te doorlopen en ik ben dankbaar voor alles wat ik in deze periode heb geleerd.

Lieve paranimfen, Bregje en Emmy, wat een voorrecht dat jullie naast mij staan. Ik ben ontzettend dankbaar voor jullie steun én vriendschap.

Lieve **Bregje van Swaaij**, wij begonnen dit avontuur samen en het voelt dan ook meer dan passend om het samen af te sluiten. Jouw geduld, doorzettingsvermogen en positiviteit zijn ongekend. In tijden van twijfel of stress wist jij altijd kalmte te brengen die mij hielp om alles weer in perspectief te zien. Onze gesprekken gaven mij niet alleen nieuwe energie, maar ook waardevolle inzichten. Jouw precisie en gestructureerde aanpak zijn een enorme kracht, en ik

bewonder hoe je altijd alles tot in de puntjes op orde hebt. Twijfel niet aan jezelf, want je bent meer dan klaar voor wat er komen gaat. Ik kijk ernaar uit om jou diezelfde steun terug te geven. Ik weet zeker dat jij volgend jaar zult stralen!

Lieve **Emmy Windhorst**, jouw humor en energie hebben mijn laatste jaar echt opgevrolijkt. Jij zorgde ervoor dat ik naast het harde werken ook momenten van ontspanning en relativering had. Het voelde alsof ik met jou altijd de ruimte had om mezelf te zijn, ongefilterd en zonder oordeel. Onze gesprekken en gedeelde momenten hebben deze tijd een stuk gezelliger én waardevoller gemaakt. Dankjewel voor je aanstekelijke lach, je steun en voor alles wat je mij hebt geleerd. Je bent een groot voorbeeld!

Lieve **Maud Joosstens**, zonder jou is de club niet compleet. Ik ben ontzettend blij dat ik een deel van dit avontuur met jou heb mogen delen. Je hebt de gave om mensen op hun gemak te stellen. Ik hou van je open, nuchtere blik en bewonder de manier waarop je in het leven staat. Dankjewel dat je me op die manier ook hebt weten te inspireren.

Lieve **dr. Thérèse Elkerbout**, wat ben jij een voorbeeld voor ons allemaal. Je bent altijd bereid om jouw kennis en ervaring te delen. Je bent niet alleen een geweldige bron van advies, maar ook een steunpilaar binnen onze groep. In datzelfde kader wil ik ook mijn dank uitspreken aan **dr. Eveline van der Sluijs**. Je bent een lieve en waardevolle collega, maar nu ook nog mijn opponent tijdens de verdediging. Het is bijzonder om te weten dat de persoon die mijn werk kritisch zal beoordelen, ook iemand is die ik ontzettend waardeer. Ik wil je nogmaals persoonlijk bedanken voor jouw bijdrage aan dit proefschrift.

Een speciaal woord van dank aan al mijn co-auteurs en in het bijzonder aan dr. Cees Valkenbrug, Tim Thomassen, Max Schoenmakers, Eveline Willems en dr. Laura Žiūkaitė. Dank voor jullie waardevolle bijdrage en samenwerking. Jullie zijn hét voorbeeld voor een succesvolle samenwerking met een mondhygiënist!

Lieve Sonja Kalf, Julie Graswinckel, Yinli Liu, Marion Seuntjens, Anouk Loeffen en Lars Toonen, jullie aanwezigheid maakt een dag op ACTA of een congres altijd een stuk leuker. Dagen met jullie zijn niet alleen leerzaam, maar ook gevuld met veel plezier en gezelligheid. Dank jullie wel voor de fijne sfeer die jullie meebrengen.

Bedankt oud-MKA-collega's van het **Amsterdam UMC** voor de betrokkenheid en samenwerking de afgelopen jaren. De kennis en ervaring die ik daar heb opgedaan, neem ik mee in deze nieuwe fase. Ik heb veel van jullie geleerd en ik ben dankbaar voor de tijd die wij samen hebben gedeeld. Collega's van het **Kennisinstituut**, bedankt voor jullie warme welkom en de support van de afgelopen maanden. Het voelt goed om deze nieuwe stap te zetten en onderdeel te zijn van zo'n enthousiaste organisatie.

Mijn dank gaat ook uit naar **Human Concern**, voor hun waardevolle steun in een belangrijke fase van mijn leven.

Lieve familie en vrienden, ongelofelijk bedankt voor de steun en adviezen die ik heb gekregen.

Ten eerste wil ik mijn lieve vriendin **Sanne** bedanken. Jij bent hét creatieve brein achter dit boekje. Ik waardeer je passie en toewijding die je in dit project hebt gestoken. Je hebt mijn visie tot leven gebracht en uitgedrukt in dit proefschrift. Daarnaast wil ik je bedanken als vriendin. Jouw steun en aanmoediging zijn van enorme waarde voor me geweest. Mijn lieve **vriendengroep uit Enschede,** bedankt! Jullie zijn al jaren een belangrijk deel van mijn leven, en ik ben ontzettend dankbaar voor jullie vriendschap en steun. Jullie hebben mij altijd gemotiveerd en opgevrolijkt, ook tijdens uitdagende momenten in mijn leven. Daarnaast wil ik mijn jaarclub **Buzz** en de **Admiraal** bedanken. In mijn studententijd heb ik verrassend genoeg toch de basis gelegd voor deze bijzondere dag. Jullie zijn stuk voor stuk een bron van inspiratie en ik ben dankbaar dat ik deze mijlpaal met jullie kan vieren.

In het bijzonder wil ik een paar woorden richten tot iemand die als rode draad door mijn leven loopt, mijn lieve vriendin **Fabiënne**. Dankjewel voor je vriendschap, je steun en je vele wijze woorden die je met mij hebt gedeeld. Je bent een onmisbare schakel in elke fase van mijn leven. Dankjewel voor alles wat je voor mij doet.

Lieve Caroline, Peter, Maarten, Monique, Marieke en Mathijs dank voor jullie nuchtere Rotterdamse blik en het zijn van mijn bonus-familie. Jullie steun betekent enorm veel voor mij.

Lieve mama en papa, jullie zijn altijd mijn grootste supporters geweest. Mijn zorgenloze en liefdevolle jeugd bij jullie heeft de perfecte basis gevormd voor de rest van mijn leven. Nu nog steeds is het fijn thuiskomen, wetende dat jullie altijd voor mij klaar staan. Zonder jullie onvoorwaardelijke steun was dit proefschrift er niet geweest. Dank jullie wel voor jullie geduld, opofferingen en alles wat jullie voor mij doen. Heel veel dank voor alles, jullie zijn geweldig. Wessel, mijn lieve broer(tje). Jouw aanmoediging en geloof in mij betekenen veel, en ik ben zo dankbaar dat ik jou als broer heb. Je herinnert mij vaak aan het belang van plezier maken en het genieten van het leven. Laten we dat vooral blijven doen! Lieve Britney, dankjewel voor de warmte die je in ons gezin brengt, en voor je steun aan Wessel. Jullie twee zijn een geweldig team!

Lieve lieve Hein, nu we dit hoofdstuk afsluiten, weet ik het zeker: samen kunnen wij de wereld aan! Wat hebben we veel meegemaakt tijdens dit avontuur, maar iedere ervaring heeft ons dichter bij elkaar gebracht. Met jouw aanmoediging en positieve kijk op het leven heb je mij geïnspireerd om elke uitdaging met open armen aan te gaan. Dankzij jou ben ik sterker geworden en heb ik geleerd nog meer te genieten van het leven. Ik wil je bedanken voor de ruimte die je mij geeft, voor het vertrouwen en de vrijheid om mezelf te zijn en voor alles wat je elke dag opnieuw doet. Met heel veel liefde kijk ik uit naar de toekomst die wij samen zullen opbouwen, want ik weet dat we alles aankunnen zolang we maar samen zijn. Jij maakt mijn leven compleet! Door dik en dun en voor altijd, love you.

Ließ Whe !

"In time, she'll find
This was so kind
So long, dance on
She's gone, dance on"

Disclosure

