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Diabetes, smoking and family history

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PERIODONTOLOGY

Laura Žiūkaitė

Risk factors of periodontitis

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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 (VU), The Netherlands.

ACTA

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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
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in het openbaar te verdedigen in de Agnietenkapel
op woensdag 03 mei 2023 te 13.00 uur

door

Laura Žiūkaitė
geboren te Kaunas

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Faculteit der Tandheelkunde

For Vincent.

Paranimfen:
Jan Albertus Hylarius Tromp
Arjan de Meij

The Japanese word for a circle

is enso [formally spelled ensō].

It is a universal expression of wholeness

that lives deep in our beings.

This symbol was carefully chosen to acknowledge
that the findings of this doctorate thesis
may be seen in the entirety.

Table of contents

General introduction

Periodontitis

Periodontitis is a chronic, multifactorial inflammatory disease of the tooth-supporting tissues that is characterized by progressive destruction of alveolar bone and connective tissue tooth attachments. If left untreated, this destruction can result in irreversible periodontal attachment loss, tooth mobility, and eventually tooth loss (Kinane et al., 2017; Könönen et al., 2019; Pihlstrom et al., 2005). Periodontitis together with caries is the leading cause of tooth loss and is regarded as one of the most serious threats to oral health. It has a negative impact on masticatory function, nutrition status, self-esteem, social conditioning, and overall quality of life (Kinane et al., 2017; Pihlstrom et al., 2005; Tonetti et al., 2017). With a periodontitis prevalence ranging from 20% to 50% according to the Global Burden of Disease Study (2016), it is worldwide the sixth most prevalent disease. The severe form of periodontitis was ranked as the 11th most prevalent condition in the world (Nazir et al., 2020; Sanz, 2010; Vos et al., 2017). In fact, the World Health Organization's (WHO) 2022 global oral health status report identifies severe periodontal disease as a major oral disease with a growing global burden, with an estimated one billion cases worldwide in 2019 (WHO, 2022). In Western Europe, the region which offers some of the most advanced healthcare services to their population, it is believed that the prevalence of periodontitis has remained largely unchanged over the last 25 years. However, a recent systematic review on worldwide studies published between 2011 and 2020 showed that periodontitis in adults was estimated to be around 62%, and severe periodontitis approximately 24% (Trindade et al. 2023). Developments in the prevention and management of periodontitis appear stagnant. Also, despite the fact that dental care in the Netherlands prioritizes quality, safety, and oral disease prevention, the prevalence of severe periodontitis among dental patients has been reported to be 16.2% (Beukers et al., 2016; den Boer et al., 2020; Leung et al., 2022).

Periodontitis affects people of all ages, but prevalence increases gradually with age, with an incidence peak around the age of 38 (Kassebaum et al., 2014). Given the disease progression's severity with age, it is most prevalent among adult-aged populations, primarily elderly patients, depicting the cumulative effects of long-term exposure to established risk factors (Arigbede et al., 2012; Botero et al., 2014; Nazir et al., 2020; Susin et al., 2014). In accordance with this, an epidemiological study found that the elderly population had the highest prevalence of chronic periodontitis (82%), followed by adults (73%) and adolescents (59%) (Tadjoedin et al., 2017). Several etiological factors have been identified that influence the onset and progression of periodontitis. Bacterial colonization of surfaces in the oral cavity is considered a primary cause (Bartold & Van Dyke, 2013; Kinane et al., 2017; Nazir et al., 2020; Shi et al., 2015). In addition, there are modifiable risk factors (i.e., amenable to intervention) like smoking, poor oral hygiene, diabetes, and hormonal

changes, as well as non-modifiable risk factors like age and heredity (Kinane et al., 2006; Kinane et al., 2017). A proper understanding of potential risk factors and of the correlation between systemic diseases and periodontal health might aid in identifying susceptible individuals prior to the onset of periodontal disease, which in turn may help to prevent or slow its progression (Reynolds, 2013).

A Risk

Given the diversity of scientific disciplines, there is no consensus in the scientific literature regarding a definition for the term "risk" (Aven, 2012; Jedynak & Bąk, 2020). Some definitions are expressed in terms of probabilities, others in terms of uncertainty and expected values, triggering events or consequences, or objectives (Jedynak & Bąk, 2020). In the context of medicine, risk is defined as the probability (Arnold, 2005; Aven & Renn, 2009) that an event will occur in the future, such as the probability that an individual with a specific risk factor will develop a particular disease (Beck, 1994; Rendón-Macías et al., 2021). In the regard of medical risk, three types of risk variables are important, and these can be categorized into three major groups. The **first** group comprises risk factors or factors that have been linked to an increased probability of disease and are thought to play a role in its etiology, such as a person's exposure to a specific bacterium (Beck, 1994; Nexøe et al., 2007; Van der Velden et al., 2006). The **second** group comprises risk determinants, which are background characteristics that are not thought to be aetiologic and are amenable to intervention, such as age, gender, and race (Beck, 1994; Van der Velden et al., 2006). The **third** group of variables comprises risk predictors, which are used to predict a person's risk of an event either quantitatively (such as with biological markers like cholesterol measurement) or quantitively (such as with historical measures like family history of disease) (Janes et al., 2008; Van der Velden et al., 2006).

Diabetes

Diabetes is a chronic metabolic disorder characterized by elevated blood glucose levels or hyperglycemia, resulting from abnormalities in insulin secretion, action, or both (Casanova et al., 2014; Sameer et al., 2020). Diabetes, if poorly controlled, is considered a risk factor for periodontitis (Tonetti et al., 2005). The incidence and prevalence of diabetes have increased dramatically over the past few decades, making it one of the most challenging global health problems. In 2019, diabetes was estimated to affect approximately 463 million adults aged 20 to 79 years,

accounting for 9.3% of the global adult population. Remarkably, estimates show that by 2030 this number will rise to 578 million, or 10.2%, and by 2045 it will rise to 700 million, or 10.9% (Saeedi et al., 2019; Sameer et al., 2020). Based on its etiology and pathogenesis, diabetes is classified into several types, the most prevalent of which are type 1 diabetes mellitus (T1DM); type 2 diabetes mellitus (T2DM); gestational diabetes (i.e., hyperglycemia during pregnancy); and other types, including diabetes caused by specific conditions like hormonal disturbances, genetic insulin action abnormalities, or pancreatic pathologies (Casanova et al., 2014; Kharroubi, 2015; Sameer et al., 2020).

T1DM (formerly known as insulin-dependent DM or juvenile-onset DM) accounts for 5% to 10% of diabetes cases and is caused by impaired insulin secretion resulting from autoimmune destruction of insulin-producing pancreatic β cells (Casanova et al., 2014; Daneman, 2006; Maahs et al., 2010). Although most frequently diagnosed in children and adolescents (80%– 90%), T1DM can manifest at any age (Craig et al., 2009; Dabelea et al., 2014). T2DM (formerly known as non-insulin-dependent diabetes or adult-onset diabetes) accounts for approximately 90%–95% of diabetes cases and is caused by a decrease in the responsiveness of the body cells to insulin, which is known as insulin resistance (Casanova et al., 2014; Sameer et al., 2020). Major risk factors for T1DM include genetic predisposition and environmental triggers like viral infections rather than lifestyle factors (Casanova et al., 2014). In contrast, T2DM is typically associated with lifestyle factors such as being overweight/obesity and lack of exercise, as well as genetic factors. Although T2DM is most commonly seen in people over the age of 45, its incidence is increasing in children, adolescents, and young adults due to rising levels of obesity, physical inactivity, and unhealthy dietary patterns (Casanova et al., 2014; Kharroubi, 2015). Hyperglycemia, a defining hallmark of diabetes, has adverse impacts on multiple body organs and disrupts their normal functioning. This disruption can cause organ damage, particularly in the eyes, kidneys, heart, and nerves (Rawshani et al., 2017; Sameer et al., 2020).

The Diabetes–Periodontitis Relationship

The onset and severity of periodontitis have both been linked to diabetes, and a "two-way" correlation between diabetes and periodontitis has been suggested. Studies have demonstrated that persistent hyperglycemia resulting from uncontrolled diabetes increases the risk for periodontitis by two to threefold compared to the risk of patients with controlled diabetes (Casanova et al., 2014; Mealey & Ocampo, 2007; Preshaw et al., 2011). Although the precise mechanisms underlying the association between diabetes and periodontitis are not fully understood, multiple factors have been proposed, including

immune functioning and inflammation, neutrophil activity, and cytokine biology (Casanova et al., 2014; Preshaw et al., 2011; Taylor et al., 2013). Studies have also shown that chronic periodontitis and periodontal inflammation can negatively affect patients with diabetes. People with advanced periodontitis were found to have a higher prevalence of diabetes complications, such as cardiovascular complications, retinopathy, and neuropathy (Casanova et al., 2014; Lalla & Papapanou, 2011; Taylor et al., 2013). While there is a large body of literature that discusses the risk factors that contribute to both diseases and that explains the underlying biological mechanisms, the vast majority of papers discuss risk factors separately in the context of either periodontitis or diabetes. Intriguingly, there is a summary of modifiable and non-modifiable risk factors that are common for both periodontitis and diabetes (Borgnakke 2016a, 2016b). The most common modifiable factors include smoking status, hyperglycemia, hyperlipidemia, being overweight/obesity, microbial overgrowth/infection/inflammation, unhealthy dietary patterns, and sedentary lifestyle, among others. Furthermore, age, gender, race/ethnicity, socioeconomic status, certain systemic conditions, genes, family history of diabetes complications, and smoking history are the most common shared factors (Borgnakke, 2016a).

Smoking

Tobacco smoking is the act of burning tobacco and inhaling the smoke, which can then be absorbed into the bloodstream (Ford & Rich, 2021; Stratton, 2001). Tobacco smoke contains over 4,000 different toxic substances, including benzanthracene, hydrogen cyanide, and the alkaloid nicotine, the latter of which is the most responsible for addiction to smoking (Bánóczy et al., 2001; Stratton, 2001). Smoking is considered an established risk factor for periodontitis. About 23% of the global population smokes cigarettes (including 32% of all males and 7% of all females), with Eastern and Southeast Asia having the highest prevalence of smokers at around 45%, and the Caribbean and North America having the lowest prevalence at 20% (Gowing et al., 2015). A large body of evidence shows that smoking cigarettes is associated with increased all-cause mortality and is a major risk factor for a variety of chronic diseases, such as cardiovascular disease, various cancers, and lung diseases (Onor et al., 2017; Patel et al., 2008). Cigarette smoking is considered one of the most significant, well-established risk factors impacting the prevalence, extent, and severity of periodontal diseases, and it is the strongest factor among the modifiable factors, with studies demonstrating that smokers are three times likelier than non-smokers to have a severe form of periodontal disease (César Neto et al., 2012; Johnson & Hill, 2004; Zhang et al., 2019). Accordingly, it has been established that the decline in smoking rates is

linked to a corresponding decline in the prevalence of periodontal disease (Bergström, 2014; Hujoel et al., 2003). Similarly, studies have found that smokers have significantly more alveolar bone loss, a higher prevalence of tooth loss, and poorer outcomes from all types of periodontal treatments than non-smokers (Albandar et al., 2000; Ojima & Hanioka, 2010; Sanz et al., 2010; De Wet et al., 2018; Van der Weijden et al., 2019). Evidence indicates that smoking alters the function and growth of periodontal cells, including gingival fibroblasts, periodontal membrane cells, and periodontal ligament cells, among others (Alamri et al., 2014; Bergström, 2014). It has also been suggested that smoking inhibits autoimmune defense; exacerbates inflammation responses; and alters the oral microbial flora, which increases the level of certain periodontal microorganisms and affects the host response (César Neto et al., 2012; Zhang et al., 2019). In fact, the subgingival microflora in smokers is characterized by a pathogen-enriched community, which has a lower resilience compared to that of nonsmokers; this, combined with an ineffective host immune response, may contribute to alterations in the subgingival microflora in smokers, increasing the difficulty of treatment (Jiang et al., 2020).

Consequently, smoking contributes to the onset, progression, and severity of periodontal disease through a variety of mechanisms: (1) decreased gingival perfusion, which limits the delivery of nutrients and oxygen and the removal of waste products; (2) suppression of the immune response, particularly inflammation and oxidative stress; (3) suppression of the periodontium's morphological and functional recovery; and (4) dysbiosis and increased infectivity of the oral microbiota (Bergström et al., 2000; Silva, 2021). These factors impair wound healing, increase the risk of complications, and hasten the progression of periodontal disease. In light of the existing evidence, it can be concluded that smoking is associated with an increased risk of periodontal disease. However, further research is needed to determine the precise mechanisms by which tobacco use promotes periodontal destruction (César Neto et al., 2012).

Genetics of Periodontitis

In the oral cavity, genes play a significant role in regulating the complex interaction between the immune system, microbiota, and lifestyle habits (oral hygiene self-care, smoking, stress, diet, etc.) that necessitate adaptation of the host's physiology to maintain health. Genetic predisposition is considered a risk determinant for periodontitis and is believed to play an important role in both the disease’s onset and progression (Van der Velden et al., 2006). Some individuals are more predisposed to developing the disease than others, and studies have indicated that periodontitis' heritability can reach up to 50% (Borrell & Papapanou,

2005; Kinane et al., 2017). Periodontitis is a chronic inflammatory disease marked by immune dysregulation, with subgingival biofilm and its antigenic products triggering the inflammatory response. While both environmental and genetic factors play a role in the development and progression of the periodontitis, genetic variability in the host ultimately determines the host's susceptibility to disease development and the rate at which a disease progresses (Schäfer et al., 2010; Da Silva et al., 2017). Furthermore, a genetic predisposition to a clinical phenotype is the result of variations in many genes encoding different proteins; genetics influence host response, and any genetic defects or alterations can increase the prevalence of periodontal disease and may be responsible for periodontal disease progression. As a result, the gene is regarded as a factor in periodontal disease because the physiological process it induces is linked to the occurrence and severity of the disease (Grace Umesh et al., 2022). Hence, the host response blueprint may determine how the immune system adapts to a wide range of situations by creating, maintaining, and controlling adequate immune responses. It can range from normal tolerance and homeostasis with the dental biofilm to an imbalance with the dental biofilm that causes inflammation-driven destruction of periodontal tissues and, ultimately, periodontitis (Loos & Van Dyke, 2020). Moreover, given the significance of the immune system in the pathophysiology of periodontal disease, research focuses on identifying genetic mutations or polymorphisms associated with the different aspects of immunity. Depending on the severity of the infection and the susceptibility of the host, the effects of these genetic variations can be subtle or profound; this is why research into the genetic basis of periodontal disease is so significant (Grace Umesh et al., 2022).

Family History

In the scientific world, family patterns of disease have been analyzed to study different forms of periodontitis. The twin study designs has been used to investigate periodontitis in this respect. Although these approaches allow tests of hypotheses to be conducted regarding disease heritability and mode of transmission, they do not identify the specific genes involved (Carvalho et al., 2009; Marazita et al., 1994; Research, Science and Therapy Committee of American Academy of Periodontology, 2005). It remains challenging to use a familial study design to distinguish between the relative contributions of genetic versus environmental factors to disease susceptibility. However, family/parental history of periodontal health appears to be a valid representation of the complex interplay between shared genetic factors and shared environmental factors, exposures, and behavioral risk factors such as level of education, socioeconomic status, oral hygiene, possible bacterial transmission, diseases like polygenic

disorders, passive smoking, pollutant exposure, and sanitation that contribute to an individual's periodontal health (Grace Umesh et al., 2022). In light of the above points, family history is considered a risk predictor.

To understand intergenerational succession in periodontal health, a study whether an individual's periodontal health and disease risk are predicted by those of their parents (Shearer et al., 2011). The results revealed that parents with poor periodontal health tended to have offspring with poor periodontal health. Notably, predictive validity was enhanced when information was available from both parents. A recent literature review regarding family history of periodontal disease in children and concluded that children whose mothers had a periodontal condition were more likely to have periodontal illnesses, particularly gingivitis (Alanazi et al., 2022).

Research statement

This thesis assesses the prevalence of risk factors among a population of patients with periodontitis, namely focusing on diabetes, smoking, and family history. Moreover, it details how diabetes might be associated with tooth loss and edentulism. In terms of research design, systematic reviews and retrospective analysis were used.

This thesis addresses the following research questions:

- What is the prevalence of diabetes among adult periodontitis patients in the Netherlands?
- Based on a systematic review, what is the global prevalence of diabetes in people clinically diagnosed with periodontitis?
- Based on a systematic review, what is the risk of tooth loss in patients with diabetes?
- Based on a systematic review, what is the risk of edentulism in patients with diabetes?
- What is the prevalence of smoking status and family history of periodontal disease among adult periodontitis patients in the Netherlands?

The majority of the chapters in this thesis have already been published in scientific dental journals. As some of the studies concern a similar topic there are inevitably considerable overlaps between chapters. Different journal requirements have also created some variations in terminology from one chapter to the next. For editorial reasons, the chapters in this thesis are not arranged chronologically.

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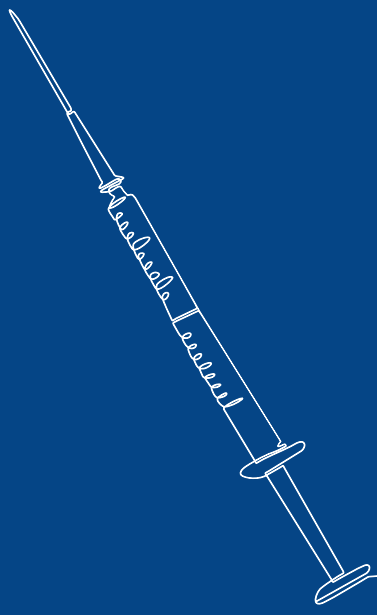
Intelligence is the ability to adapt to change.

Stephen Hawking



Chapter 1

Prevalence of diabetes among patients diagnosed with periodontitis:

A retrospective cross-sectional study.

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ORIGINAL ARTICLE

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Prevalence of diabetes among patients diagnosed with periodontitis: A retrospective cross-sectional study

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Abstract

Objective: The objective of this study was to assess the prevalence of diabetes among patients with periodontitis and to evaluate whether diabetes is related to extent and severity of periodontitis.

Method: This is a retrospective study of data observed over a 10-year period in patients referred to a specialized clinic for periodontology in the Netherlands. Patients received at the intake appointment a full-mouth periodontal examination, and based on the clinical data, patients were classified with respect to extent and severity of periodontitis. In addition, the prevalence of diabetes was recorded, based on self-report.

Results: A total of 5375 periodontitis patients were included in the study sample (mean age of 50 years). The prevalence of diabetes in this patient sample was 3.7% (n=192). No relation between diabetes and extent or severity of periodontitis could be established.

Conclusion: The prevalence of diabetes in a predominantly "controlled" diabetic population was not related to the extent and/or severity of periodontitis along with the finding that the prevalence was lower than the national diabetes prevalence in the Netherlands.

KEYWORDS
diabetes, periodontal disease, periodontitis, risk factors, risk indicator

1 | INTRODUCTION

Periodontitis is a destructive inflammatory disease affecting both the soft tissues and bone that surround and support the teeth. A recent epidemiologic survey reported that periodontitis affected approximately 47% of adults age ≥30 years and 64% of those >65 years old.[1] As defined by loss of bone and clinical attachment level, severe periodontitis impacts roughly 5% to 15% of adults.[1,2] A dysbiotic oral microbial flora and dysregulated immune-inflammatory processes are responsible for the majority of the host tissue destruction and ultimate tooth loss.[3] However, the disease is multifactorial and severity and progression of symptoms may also be influenced by genetic, epigenetic and lifestyle risk factors.[4-6] Epidemiological studies have reported a relationship between increased severity of periodontitis and type 2 diabetes mellitus.[7-9] Manifestation of periodontal disease in diabetic patients has been associated with age of onset, gender, duration of diabetes, poor metabolic control and diabetes-related complications.[10] Indeed, Khader et al. conducted a systematic review of the literature and meta-analysis involving 21 studies and reported that diabetic patients, in general, had a higher severity of periodontal disease than non-diabetics.[11] Other studies have noted that patients with controlled diabetes exhibit a periodontal status comparable to that of the general population.[12,13] The joint workshop of the European Federation of Periodontology and the American Academy of Periodontology concluded that there is consistent and robust evidence that severe periodontitis adversely affects blood glucose levels.[3] Also, moderate-to-severe periodontitis is associated with an increased risk for the development of diabetes. Evidence supports a dose-dependent role of periodontitis for diabetes complications.[3]

The guidelines for physicians and other medical health professions that emerged from this International workshop state *"Patients with diabetes should be told that periodontal disease risk is increased by diabetes. They should also be told that if they suffer from periodontal disease, their glycemic control may be more difficult, and they are at higher risk for diabetic complications"*.[3] Hence, in the third revision published in 2013 of the diabetes care protocol of the Dutch Society of General Physicians, an item has been added that recommends an oral inspection for signs of periodontitis during the yearly check-up of diabetes patients.[14,15]

There are few studies that address the prevalence of diabetes in patients referred to a specialty clinic for treatment of periodontitis. Given the purported bidirectional relationship between diabetes on periodontitis,[16-20] the aim of this study was to conduct a retrospective study to investigate the prevalence of diabetes in a referred population of periodontitis patients and to determine whether diabetes is related to extent and severity of periodontitis.

2 | MATERIALS AND METHODS

This report was prepared according to the guidelines suggested by the STROBE checklist.[21,22] The checklist recommends items that should be included in reports of observational studies (Appendix S1). Further, it should be noted that because all data were procured from treatment records of private practice patients, approval by an Institutional Review Board for Human Research was not required for this study.[23]

2.1 | Data set of the studied population

This retrospective cross-sectional study utilized treatment records of patients referred to a private periodontics specialty practice in the city of Utrecht, the Netherlands. The data were extracted from the treatment records of patients seen between the years 2003 and 2014 for periodontal examination. It was the customary and a standard procedure in the private practice to verbally confirm all positive responses on the patient's medical history document. Consecutive subjects having both a diagnosis of periodontitis and a completed questionnaire were considered as eligible for the study.

2.2 | Periodontal diagnosis

Full-mouth periodontal examinations were performed by a trained and experienced periodontist. Measurement and recording of clinical parameters included the following: missing teeth, gingival recession, probing pocket depth, clinical attachment loss, tooth mobility, furcation involvement and bleeding upon probing. These data in combination with a full set of dental radiographs were used to classify each patient according to the criteria as proposed by Van der Velden.[24,25] This classification system expresses the extent of periodontal disease by taking into consideration the number of affected teeth. The severity of disease is based on the amount of bone loss or clinical attachment loss (see Table 1 for details of classification).

2.3 | Data extraction

Based on the clinical examination, data of patients were coded in numbers to simplify future analysis. Data included patients' demographics, periodontal diagnosis,[25] smoking status and diabetes.

2.4 | Data analysis

Using the Van der Velden[25] classification of periodontitis, groups were dichotomized for groupwise comparisons as follows: less

TABLE 1 Classification of periodontitis to Van der Velden.[25] Adapted from: Van der Velden U. Purpose and problems of periodontal disease classification. *Periodontol.* 2000;2005:13-21.[25]

Classification of periodontitis based on the extent of disease. If teeth are missing, the class description should still reflect the clinical image of the patient. Therefore, for cases with ≤14 teeth the class semi-generalized is omitted and the number of teeth for the generalized category is changed from 8 to 14 teeth.			
	Permanent/mixed dentition number of teeth present		
	n=≥14	**n=≤14**	**Primary dentition**
Incidental	1 tooth	1 tooth	1 tooth
Localized	2-7 teeth	2-7 teeth	2-4 teeth
Semi-generalized	8-13 teeth	–	5-9 teeth
Generalized	≥14 teeth	8-14 teeth	≥10 teeth
Classification of periodontitis based on the severity of disease per tooth. The mean estimated root length, based on the literature, is approximately 12 mm; in the case of incidental disease, the severity category at that particular tooth is mentioned.			
Minor	Bone loss ≤1/3 of the root length or attachment loss ≤3 mm		
Moderate	Bone loss >1/3 and ≤1/2 of the root length or attachment loss 4-5 mm		
Severe	Bone loss >1/2 of the root length or attachment loss ≥6 mm		

TABLE 2 Prevalence of diabetes with demographic characteristics and their distribution among the three categories of severity of periodontitis and the four categories of the extent of periodontitis

	Prevalence (%) among severity categories		
	Less severe (n=1025)		More severe (n=4350)
	Minor n=213	Moderate n=812	Severe n=4350
Age			
≥35 to ≤45	20.2	15.8	14.4
>45 to ≤55	23.0	29.2	31.1
>55	56.8	55.0	54.5
Gender			
Female	64.3	60.5	53.3
Male	35.7	39.5	46.7
Diabetes mellitus	1.4	3.1	3.8

	Prevalence (%) among extent categories			
	Smaller extent (n=1830)		Higher extent (n=3551)	
	Incidental n=236	Localized n=1594	Semi-generalized n=1047	Generalized n=2504
Age				
≥35 to ≤45	20.3	16.9	13.1	13.7
>45 to ≤55	30.1	31.4	32.3	29.2
>55	49.6	51.8	54.6	57.1
Gender				
Female	69.9	60.3	57.0	49.0
Male	30.1	39.7	43.0	51.0
Diabetes mellitus	4.2	3.1	3.3	3.9

severe (minor and moderate severity) and more severe (severe disease); and smaller extent (incidental and localized periodontitis lesions) and higher extent (semi-generalized and generalized periodontitis lesions). The ratio of the total number of periodontitis patients without diabetes to the number of periodontitis patients with diabetes (prevalence) was calculated. The relation between the presence of dichotomous factors (diabetes, gender) and extent or severity of periodontitis was first assessed by means of contingency tables. For the continuous risk factor (age), data were summarized by means of number of patients, mean, standard deviation, minimum and maximum. In a second step, confirmatory statistical analysis was performed by means of a generalized linear model using a logit link with each prevalence variable modelled as a binary outcome and each risk factor individually aiming to test the hypothesis. Every *P*-value is linked to a hypothesis that has to be confirmed or not. If a relation was significant, groupwise comparisons were made between the groups of the discontinuous factors indicators and *P*-values were corrected for simultaneous hypothesis testing according to Tukey. The regression coefficient of the continuous variables was used as an indicator of the direction of the relation between the continuous variables and the prevalence factors.

3 | RESULTS

3.1 | Demographic characteristics and prevalence data

Overall, the records of 5375 patients with a complete data set were included in the study. The mean age was 50 years which ranged from 35 to 94 years. The gender distribution was 54.7% females (n=2946) and 45.3% males (n=2429). In total, 3.7% of the patients self-reported by a positive reply on the medical history form (confirmed verbally) to have a condition of diabetes (n=192) (Table 2).

The prevalence of diabetes in relation to periodontitis severity categories is presented in Table 2. Of the 5375 patients, 4350 were diagnosed with the severe form of chronic periodontitis and consisted mostly of patients older than 55 years of age and with a higher prevalence of females than males (Table 2).

Prevalence of diabetes varied among the three levels of severity (i.e minor, moderate and severe) from 1.4% to 3.8%. Additionally, Table 2 also provides the information regarding the prevalence of diabetes in relation to the distribution of periodontitis (i.e extent). Almost half of the patients had a generalized periodontitis (n=2504). Gender

TABLE 3 Distribution (predictive value percentage) of diabetes and demographic characteristics between two categories of severity and two categories of the extent of periodontitis

	Predictive value percentage		
	Less severe periodontitis (n=1025)	More severe periodontitis (n=4350)	*P*-value for relation
Age			.1051
≥35 to ≤45	21.2	78.8	
>45 to ≤55	17.4	82.6	
>55	19.3	80.7	
Gender			<.001*
Female	21.3	78.7	
Male	16.3	83.7	
Diabetes	14.6	85.4	.1087
	Predictive value percentage		
	Smaller extent periodontitis (n=1830)	Higher extent periodontitis (n=3551)	*P*-value for relation
Age			<.0006*
≥35 to ≤45	39.7	60.3	
>45 to ≤55	34.8	65.2	
>55	32.0	68.0	
Gender			<.001*
Female	38.2	61.8	
Male	28.9	71.1	
Diabetes	30.7	69.3	.3293

*Significant.

was evenly dispersed over the four categories of disease distribution, that is incidental, localized, semi-generalized and generalized. More than half of the patients in the generalized periodontitis group were >55 years. Diabetes prevalence varied among the four categories of disease distribution from 3.1% to 4.2%.

3.2 | Groupwise comparisons of diabetes predictive values and demographic characteristics categorized by severity and extent of disease

As shown in Table 3, the age of the patient in the sample population, assessed using three defined age groups, was not significantly related to disease severity (*P*=.1051). The predictive values of being diabetic between the two severity categories (moderate and severe) also did not differ significantly (*P*=.1087). Male gender was significantly related to the severe form of adult periodontitis (*P*<.001).

The age of the patient in the sample population, assessed using three defined age groups, was significantly related to the extent of the disease (*P*=.0006). Also, male gender was significantly related to the higher extent of disease (*P*<.001). For diabetes patients, the predictive values did not differ significantly between the incidental, and localized as compared to semi-generalized and generalized extent of disease categories (*P*=.3293).

3.3 | The relation of smoking and diabetes with the extent and severity of periodontitis

Of the patients with diabetes, 26% were smokers (n=45). The possible interaction of smoking and diabetes relative to extent and severity of periodontitis was explored. This appeared not to be the case (*P*-values .853 and .9951, respectively) (see Appendix S2).

4 | DISCUSSION

The current retrospective study focused on a periodontal private practice referral population and examined the prevalence of diabetes in relation to extent and severity of chronic periodontitis. The number of study patients involved in the present study (5375) represents the largest such population in a European study and is surpassed only by one Asian study.[26] Of the 5375 study patients, 80.9% (n=4350) were diagnosed as presenting with severe chronic periodontitis and 46.5% (n=2504) with a generalized distribution of the disease. Additionally, 3.7% (n=199) of the study patients reported having diabetes on the medical history document. It was observed that the diabetes prevalence numerically increased with disease severity, 1.4%, 3.1% and 3.8% from mild, moderate-to-severe periodontitis, respectively. However, the predictive value was found not to be statistically significant. Furthermore, there appeared to be no relationship regarding the presence of diabetes and the extent (i.e distribution) of chronic periodontitis.

The degree of glycemic control is likely to be a major factor in determining risk for extent and severity of periodontitis.[10] A higher prevalence and severity of periodontal destruction have been reported in patients with poor glycemic control than in those considered well controlled.[27,28] A subanalysis of well-controlled vs poor-controlled diabetes patients was not performed in the current study due to the small number of patients reporting to be poorly controlled (n=3).

Of interest is that the prevalence of diabetes in the current study (3.7%) was less than the reported Dutch national diabetes prevalence in 2016, which ranged from 6.1% (World Health Organization, 2016) to 7.2% (International Diabetes Federation, 2014).[29,30] Also noteworthy is that according to reports of the Dutch Ministry of Health[31] based on data of Central Agency of for Statistics,[32] in the period 2008-2011, in the region where the private periodontal practice is located, and therefore, the source of patient data the prevalence of diabetes mellitus was the highest (8.6%) in the country.

In another practice-based periodontitis population, Nesse et al.[33] reported a prevalence of 5.1% for diabetes in 671 patients referred to two periodontic clinics in the Netherlands. The authors reported a higher prevalence of diabetes among periodontitis patients vs that of non-periodontitis patients. However, the prevalence of diabetes in the non-periodontitis group was approximately half of the national mean prevalence rate. This underestimation statistically results in a relative increased prevalence of diabetes in the periodontitis patient

group although the prevalence rate did not surpass the national mean of 5.6%. The results from the present paper and Nesse et al.[33] are supported by other European studies. In the United Kingdom, Soory et al.[34] and Dopico et al.[35] found the prevalence of diabetes among periodontitis patients to be 6.9% and 3%, respectively. Both were lower than the national mean diabetes prevalence rate of 7.8% according to WHO. Fardal et al.[36] in Norway found a prevalence of 2.3%, whereas Linden et al.[37] from Ireland found it to be 5.6%: both of these estimations were also lower that the reported national mean prevalence (6.6% and 7.3%, respectively). Aimetti et al.[38] found a 6.9% prevalence rate of diabetes among 568 Italian periodontitis patients, which is comparable to the WHO reported national mean diabetes prevalence of 6.7%. In contrast to the previous studies, a study from Switzerland reported the prevalence of diabetes among a sample of 130 periodontitis patients (10%) to be greater than the WHO reported national mean diabetes prevalence of 5.5%.[29] However, the Swiss study also reported an elevated 7% diabetes prevalence rate in the control group. Further, data from Georgiou et al.[39] support that the observed finding in the present study is not likely to be an underestimation as the authors reported that periodontitis patients from a private periodontal practice experienced a higher prevalence of diabetes than did patients from general practice. However, a recent study by Holm et al.[40] compared 245 periodontitis patients to 46 control patients without periodontitis and found a prevalence rate for diabetes mellitus of 3.1% (n=9) and prediabetes of 27.1% (n=79) in the aggregate of patients. The authors also reported that periodontitis patients had a higher rate of undiagnosed diabetes mellitus and prediabetes (32.7%) than did control patients (17.4%). Thus, although one might conclude the collective body of evidence indicates that the European populations do not suffer from a significant or progressive increase in the prevalence of diabetes, this conclusion may be flawed for the reason suggested by the Holm et al. study[40] and noted in the Nesse et al. study,[33] that metabolic disease among control groups may be underestimated, due to a significant number of undiagnosed patients.

An explanation as to why the dental and, more specifically, the periodontal community considers the diabetes-periodontitis bidirectional relationship to be well established may be the result of a geographic bias as the majority of studies supporting the bidirectional concept originate from countries outside of Europe. Also, the prevalence of diabetes in other continents is reportedly greater—an observation supported by the latest World Health Organization (2015) report on global diabetes; that is, prevalence for adults ≥18 years was reported to be 9.2%.[29] Obviously, the WHO prevalence rate is higher than the European national means in the studies discussed above. Study populations may also be skewed towards metabolic disease conditions. For instance, a Swiss study reported by Wick et al.[41] noted their control group had a higher prevalence rate of diabetes than the Swiss national mean. Lastly, in certain populations diabetes control may be negatively influenced by socio-economic status, living conditions, diet or access to medical care. It is well known that poorly controlled diabetes patients have more periodontal infections than those without diabetes.[42]

Epidemiological surveys have consistently shown that periodontitis is more prevalent in males than in females.[42] For decades, it has been recognized that men of all ages, race/ethnic groups and geographic locations have significantly more periodontal disease than women.[41–44] The present study sample consisted of a higher proportion of females than males. Considering the high prevalence (81%) of severe periodontitis in the investigated sample, a higher percentage of males would have been expected. Although the predictive value for males to have severe periodontitis was significantly higher than for females, the prevalence among the population was lower (45.3%). Nesse et al.[33] also observed that females were more prevalent among a sample of referred periodontitis patients than in the regular dental clinic (61% vs 48%, $P<.001$). As a likely explanation, studies conducted in Asia, Europe, Middle East and North Africa have consistently revealed that females are more informed about tooth brushing and have a higher degree of interest in oral health than males. They exhibit more positive dental health attitude and better oral health behaviour than males.[45] Therefore, the observed gender distribution which is skewed towards females most likely can be attributed to the referral bias due to a higher dental awareness and greater willingness by women to seek treatment.

A wealth of epidemiological, clinical and in vitro studies has emerged that have provided irrefutable evidence that smoking negatively impacts periodontal health and proposes mechanisms by which this may occur. Based on the database of the present study, the prevalence of smokers and the impact on extent and severity of periodontitis among this population has been reported.[46] The prevalence of smoking was 34%; 37% were never smokers and 29% reported to be past smokers. The results also showed a significantly higher predictive value for smokers to belong to a periodontitis group with a greater extent of periodontal destruction.[46]

The issue of case definitions has been and still remains a central theme in periodontology. Several classification systems have been proposed for periodontitis, and although these systems purport to address the same disease, it has been noted that they can result in identification of different subsets of individuals.[47,48] In an analysis of defining a periodontitis patient in a population of untreated adults, it was concluded that the classification system as proposed by Van der Velden[24,25] is suited for providing clinicians with a clear image of the periodontitis case.[47,48] This classification approach uses a combination of the key clinical parameters and age-specific criteria (see Table 1). The objective of the classification is to provide a simple means to differentiate between various forms of the disease. Although this approach is not widely used therefore, preventing comparisons with other studies, the Van der Velden classifications system can be used for purposes such as estimates of treatment needs, identification of risk factors and disease activity.[24,25] This paper and a recent publication from our group[46] present an initial report on the differentiation of extent and severity among a population of periodontitis patients in relation to the prevalence of putative risk factors such as age, gender, family history of periodontitis and smoking.

4.1 | Limitations

Several limitations concerning this study were identified: (i) the sample population was dependent on referral practices of general dentists.

Professional screening for periodontal disease and patients' awareness may have changed over time. This could have attributed to a referral bias. However, the large number of included patients and the periodontists' assessment of the diagnosis "chronic periodontitis" add to the generalizability of the obtained data and avoid information bias. (ii) The data that were analysed were collected from and limited to one specialist clinic for periodontology in the Netherlands. This may influence generalizability, although the outcome is supported by data from two other referral clinics located elsewhere in the Netherlands.[33] (iii) Diabetes prevalence was assessed via self-report based on a medical history form and checked verbally by the periodontist at the intake appointment. Response bias may have resulted in an underestimated prevalence.[49,50] (iv) The majority of the sample is classified as having severe periodontitis (81%). This imbalance compared to the prevalence of mild and moderate periodontitis may result in a bias of the risk assessment. (v) Based on the clinical measurements, each patient's data were classified according to the criteria as proposed by Van der Velden [25] with the respect to extent and severity of periodontitis. It would have been of interest to evaluate also correlation between clinical parameters (probing pocket depth, clinical attachment level, number or percentage of sites with bleeding on probing or probing pocket depth equal or greater than 5 mm) and diabetic status. However, this was not possible to perform because the data set that was used contained the periodontal diagnosis (under certain codes in excel sheet) given at the day of data collection, but not the actual clinical measurements. (vi) An important limitation of the study is that the information about the type and duration of diabetes is unknown. The different pathogenic mechanisms in type 1 and type 2 diabetes may have an effect on the risk of periodontal disease as well as on other comorbidities in the two groups of patients. Type 2 accounts for 90-95% patients with diabetes. Considering the average age of the investigated patients in our study, the most likely diagnose for most of them is possibly type 2 diabetes mellitus.

5 | CONCLUSION

The prevalence of diabetes in a predominantly "controlled" diabetic population was not related to the extent and/or severity of periodontitis along with the finding that the prevalence was lower than the national diabetes prevalence in the Netherlands.

6 | CLINICAL RELEVANCE

6.1 | Scientific rationale for the study

The periodontal literature reports a bidirectional relationship between diabetes and periodontitis. Thus, it is of interest to assess the prevalence of diabetes in a population of patients that have been referred to a clinic specializing in periodontics.

6.2 | Principal findings

The prevalence of diabetes, determined by self-report, in this patient sample was 3.7%. This is lower than the estimated national diabetes prevalence in The Netherlands (range of 5.6% to 7.5%).

6.3 | Practical implications

As the prevalence of diabetes among this patient population was lower than the national diabetes prevalence rate, the metabolic state of these adult periodontitis patients does not appear to be associated with a diagnosis of periodontitis.

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CONFLICT OF INTEREST

The authors declare they have no potential conflict of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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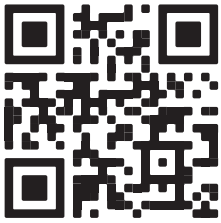
Chapter 1
Online appendices



Chapter 2

Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis:

A systematic review and meta-analysis of epidemiologic studies.

Ziukaite L, Slot DE, Van der Weijden FA.

J Clin Periodontol. 2018 Jun;45(6):650-662.

SYSTEMATIC REVIEW

WILEY Journal of Clinical Periodontology

Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies

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Abstract

Objectives: Diabetes mellitus and periodontitis are complex chronic diseases with an established bidirectional relationship. This systematic review evaluated in subjects with professionally diagnosed periodontitis the prevalence and odds of having diabetes.

Methods: The MEDLINE-PubMed, CENTRAL and EMBASE databases were searched. Prevalence of diabetes mellitus among subjects with periodontitis was extracted or if possible calculated.

Results: From the 803 titles and abstracts that came out of the search, 27 papers met the initial criteria. Prevalence of diabetes was 13.1% among subjects with periodontitis and 9.6% among subjects without periodontitis. Based on subanalysis, for subjects with periodontitis, the prevalence of diabetes was 6.2% when diabetes was self-reported, compared to 17.3% when diabetes was clinically assessed. The highest prevalence of diabetes among subjects with periodontitis was observed in studies originating from Asian countries (17.2%, *n* = 18,002) and the lowest in studies describing populations from Europe (4.3%, *n* = 7,858). The overall odds ratio for patients with diabetes to be among subjects with periodontitis as compared to those without periodontitis was 2.27 (95% CI [1.90;2.72]). A substantial variability in the definitions of periodontitis, combination of self-reported and clinically assessed diabetes, lack of confounding for diabetes control in included studies introduces estimation bias.

Conclusions: The overall prevalence and odds of having diabetes are higher within periodontitis populations compared to people without periodontitis. Self-reported diabetes 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.

KEYWORDS
diabetes, odds, periodontitis, prevalence, systematic review

1 | INTRODUCTION

Periodontitis is a ubiquitous disease affecting over 50% of the world's adult population and increases further with age (Petersen & Ogawa, 2012). Severe periodontitis, a major cause of tooth loss, is the sixth most prevalent human disease, according to the 2010 global burden of diseases study, with a standardized prevalence of 11.2% (Kassebaum et al., 2014). The most recent paper from the NHANES 2009–2012

reports almost 50% of the population aged 30–79 years old has periodontitis, with about two-thirds of seniors aged 65+ years (Eke et al., 2016). The wide range of periodontitis prevalence is not unexpected, as periodontal epidemiology has been surrounded by controversies, including disease definitions, examination protocols and units of analysis (Eke, Dye, Wei, Thornton-Evans, & Genco, 2012; Eke et al., 2015; Oliver, Brown, & Löe, 1991; Philstrom, Michalowicz, & Johnson, 2005). These and other methodological issues affect not only how data are collected, but also how epidemiological findings are reported and interpreted (Oppermann, Haas, Rösing, & Susin, 2015).

Diabetes is a chronic disease, characterized by hyperglycaemia due to a defect in insulin secretion, a decrease in insulin sensitivity, or combination of both (Borgnakke, Ylöstalo, Taylor, & Genco, 2013; Genco, 1996; Genco & Borgnakke, 2013). The reported prevalence of diagnosed diabetes differs across the world varying for instance from 4.6% in France (Bonaldi et al., 2011) to 8.3% of the entire US population or 28.8 million people. It is estimated that about 7 million are undiagnosed (Centers for Disease Control and Prevention, 2014). Diabetes is a growing public health concern globally and leads to significant mortality and morbidity associated with its major complications, such as cardiovascular disease and end-stage renal disease (Genco, & Borgnakke, 2013). Further, diabetes is continuing to be an increasing international health burden.

It is gradually becoming evident that diabetes and periodontitis are intimately intertwined and closely linked by underlying biologic mechanisms involved within each individual as a function of the interplay between innate and acquired immune responses, genetic and epigenetic factors, and external, environmental factors (Borgnakke, 2016a,b). Recently, two meticulous reviews on risk factors for both periodontitis and diabetes were published. These addressed the current belief that the host inflammatory responses overall constitute the main mechanism underlying most of the modifiable and non-modifiable risk factors for both diseases (Borgnakke, 2016a,b). Because of the similarities between those factors, they often occur in the same individuals—and also may mutually and adversely affect each other (Borgnakke, 2016a,b).

The joint International workshop of the European Federation of Periodontology and the American Academy of Periodontology concluded that there is evidence that moderate-to-severe periodontitis is associated with an increased risk for the diabetes development (Chapple & Genco, 2013). The guidelines for physicians and other medical professions state as follows: *"Patients with diabetes should be told that periodontal disease risk is increased by diabetes, and that if they suffer from periodontal disease, their glycemic control may be impaired, and they are at higher risk for diabetic complications."* Hence in the third revision (2013) of the diabetes care protocol of the Dutch Society of General Physicians, an item has been added that recommends an oral inspection for signs of periodontitis during the yearly check-up of patients with diabetes. As diabetes shares risk factors with periodontitis or interacts with its treatment, it is proposed that screening for diabetic status should be part of a standard periodontal examination (Tonetti, Jepsen, Jin, & Otomo-Corgel, 2017).

Clinical Relevance

Scientific rationale for the study: Evidence supports an increased risk for diabetes in people with periodontitis.

Principle findings: Prevalence of diabetes among subjects with periodontitis was 13.1%. Self-reported diabetes might underestimate the prevalence among subjects with periodontitis as opposed to studies that assessed the condition clinically. Geographical differences were observed, and the highest prevalence was observed in studies from Asian countries (17.2%) and the lowest in Europe (4.3%).

Practical Implications: As diabetes can go undiagnosed and the relationship with periodontitis has been established, the clinical assessment of diabetes could become a part of the standard diagnostic procedure.

Most of the recent research on the relationship between periodontitis and diabetes has focused on the impact of periodontal therapy on the glycemic control of patients with diabetes mellitus (Teshome & Yitayeh, 2016). What is currently lacking is an overall estimate of the association between being a periodontitis patient and having diabetes as based on the available published literature. Therefore, the aim of this research was to provide a comprehensive systematic review of the prevalence of patients with diabetes among subjects diagnosed with moderate-to-severe periodontitis.

2 | METHODS

The protocol of this systematic review was developed "a priori" in discussion between research group members and prepared according to MOOSE guidelines (Table S7). The focused question was as follows: "Among people that have been professionally diagnosed with periodontitis, what is the prevalence of diabetes?" Therefore, three Internet sources were used to search for appropriate papers that satisfied the study purpose. For details regarding the search terms used, see Box S1 and for search, screening and selection procedure see Figure 1, Methods S1.

The following eligibility criteria were imposed for inclusion: studies in the English language; human subjects ≥18 years old; diagnosed with periodontitis as assessed by dental care professionals; diabetes mellitus (undefined, type 1 and/or type 2) being clinically assessed or self-reported; observational study design (cohort, case–control, cross-sectional); reporting the outcome: prevalence of diabetes mellitus within a population with periodontitis.

The heterogeneity across studies was detailed according to the following factors: study design; subjects' characteristics; geographical region of the investigated population; diagnostic criteria for periodontitis; and diabetes diagnosis (Table S1). Two reviewers scored the methodological qualities (Table S3) of the included studies according to the method described in detail by Keukenmeester, Slot, Putt, and

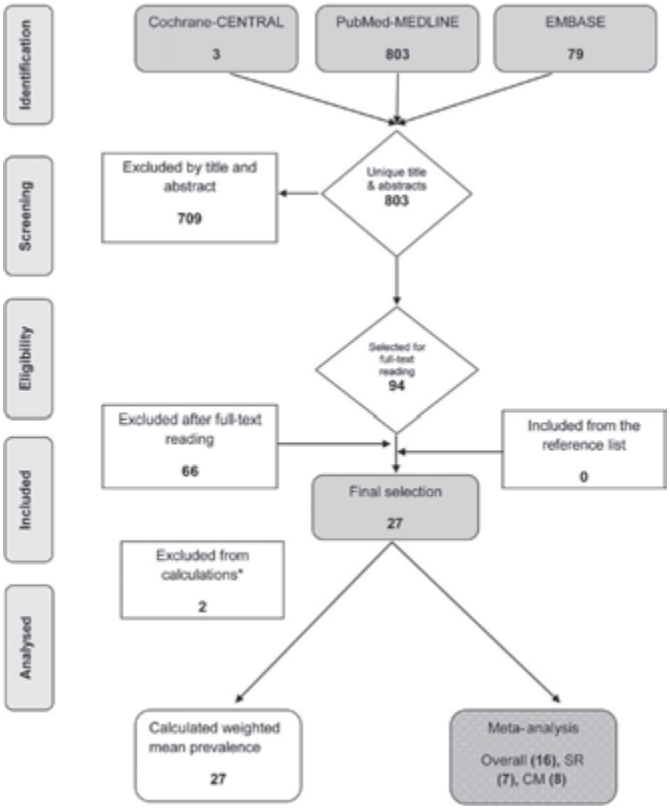

FIGURE 1 Flowchart of the procedure and the numbers of articles selected in end stage. *Papers reporting on the same study population

Van der Weijden (2013). From the papers that met the selection criteria, data were processed for further analyses (Methods S1).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, as proposed by the GRADE Working Group (2014), was used to appraise the evidence emerging from this review. Two reviewers rated the body of evidence; any disagreement was resolved after additional discussion.

3 | RESULTS

The search identified 803 unique papers (Figure 1). The screening of titles and abstracts initially resulted in 94 full-text articles of which 66 papers, after full-text reading was excluded for not meeting the eligibility criteria (Table S2). Hand searching of the reference lists revealed no additional suitable papers. Consequently, 27 studies were identified as eligible for inclusion in this systematic review (Table 1, Table S1). Several included papers published data from two national databases—NHANES and KNHANES (see selection ID: II and XIX). Studies that were conducted using the same database are listed in Table S1 with the asterisk (*). Kapellas, Skilton et al. (2014), Kapellas, Maple-Brown et al. (2014) (XII, XIII) and Torrungruang et al. (2005), Torrungruang, Bandhaya, Likittanasombat, and Grittayaphong (2009) (XXII, XXIII) published data in different papers concerning one and the same population. To avoid including the same subjects reported in different papers, the study with the highest number of participants was chosen as representative for data analysis and calculations.

The extracted data about study design, characteristics of the studied population, definition of periodontitis, diagnostic methods and criteria for diabetes and a study population location are presented in the Table S1. Evaluation of the selected papers showed considerable heterogeneity, which is described in Results S1. Quality assessment values, including methodology, external, internal and statistical validity, are presented in Table S3. Based on a summary of these criteria, the estimated potential risk of bias is low for four studies, moderate for 9 studies and high for 14 studies.

The prevalence of periodontitis among the whole studied population was 27% (Table 2). Data concerning the presence of diabetes in the population were extracted or calculated from 27 papers that altogether involved 29,594 periodontitis cases. The range of prevalence

TABLE 1 Periodontitis case definition and numbers of participants and prevalence of diabetes by periodontitis status

		With periodontitis *N* = 29,594		Without periodontitis *N* = 53,746		
Author, year (ID)	**Periodontitis case definitions**	**Participants (M/F) Age (mean, range)**	**Diabetes prevalence**	**Participants M/F Age (mean, range)**	**Diabetes prevalence**	**Type of diabetes assessment in the study**
Aimetti et al. (2015) (I)	Periodontitis: Moderate ≥2 interproximal sites with CAL ≥4 mm, or ≥2 interproximal sites with PD ≥5 mm (CDC/AAP moderate periodontitis)[b] Severe ≥2 interproximal sites with CAL ≥6 mm, ≥1 interproximal site with PD ≥5 mm (CDC/AAP severe periodontitis)[b]	568 (245/323) Mean: n/a Range: 20–75	6.9%[a]	–	–	SR: -Q -Use of diabetes medication
Al-Zahrani (2006) (II)	Periodontitis: ≥1 sites with CAL ≥3 mm and PPD ≥4 mm	1807 (n/a) Mean: 48 Range: ≥18	10.7%[a]	10,943 (n/a) Mean: 40 Range: ≥18	5%[a]	SR: -Q or INT
Al-Zahrani and Kayal (2006) (III)	Generalized periodontitis: ≥20% of bone loss in ≥30% of teeth	114 (n/a) Mean: 35 Range: 18–80	21.1%	–	–	SR: -DR
Awuti, Younusi, Li, Upur, and Ren (2012) (IV)	Periodontitis: Mild: PPD ≤4 mm, CAL 1–2 mm, moderate: gingival inflammation, BOP, PPD ≤6 mm, CAL 3–4 mm, slight mobility; Severe: inflammation, abscess, PPD >6 mm, >1 loose tooth	453 (237/216) Mean: n/a Range: ≥20	15%[a]	509 (169/340) Mean: n/a Range: ≥20	4.3%[a]	CM -Fasting venous blood glucose ≥7.0 mmol/L
Bawadi, Khader, Haroun, Al-Omari, and Tayyem (2011) (V)	Periodontitis: ≥4 teeth with 1 ≥ PPD 4 mm and CAL ≥3 mm	105 (54/51) Mean: n/a Range: 18–70	25.7%[a]	235 (114/121) Mean: n/a Range: 18–70	14.5%[a]	SR: -Q
Borges-Yanez, Irigoyen-Camacho, and Maupome (2006) (VI)	Periodontitis: Moderate: At least two sites with loss of attachment ≥4 mm, severe: at least one site had LOA ≥6 mm	135 (n/a) Mean: 73 Range: >60	29.6%[a]	122 (n/a) Mean: 72 Range: >60	20.5%[a]	CM: -World Health Organization 1985 -Fasting blood glucose value >140 mg/dl
Fardal, Fardal, and Persson (2013) (VII)	No definition	2,191/128) n/a	2.3%[a]	–	–	SR: -Q
Figueiredo et al. (2013) (VIII)	CDC/AAP moderate and severe periodontitis[b]	84 (44/40) Mean: n/a Range: 19–77	10.7%[a]	131 (52/79) Mean: n/a Range: 19–77	3.8%[a]	CM/SR: -Fasting glucose blood test (≥126 mg/dl) associated with diabetes symptoms

(Continues)

TABLE 1 (Continued)

Author, year (ID)	Periodontitis case definitions	With periodontitis N = 29,594 Participants (M/F) Age (mean, range)	With periodontitis N = 29,594 Diabetes prevalence	Without periodontitis N = 53,746 Participants M/F Age (mean, range)	Without periodontitis N = 53,746 Diabetes prevalence	Type of diabetes assessment in the study
Genco, Falkner, Grossi, Dunford, and Trevisan (2007) (IX)	CDC/AAP moderate and severe periodontitis[b]	860 (n/a) Mean: n/a Range: >24	5.9%[a]	–	–	SR: -Q
Han et al. (2009) (X)	Periodontitis: CPI ≥3	378 (214/164) Mean: 47 Range: 8–83	11.1%[a]	950 (384/566) Mean: 38 Range: 8–83	6.5%[a]	CM: -Fasting plasma glucose level ≥126 mg/dl
Heggendorn et al. (2013) (XI)	No definition	13 (n/a) Mean: 40 Range: 8–83	7.7%[a]	105 (n/a) Mean: 40 Range: 8–83	2.9%[a]	SR: -DR
Kapellas, Skilton et al. (2014) (XII)	CDC/AAP moderate periodontitis[b]	138 (77/61) Mean: 40 Range: ≥18	7.7%[a] for CM	–	–	CM: -HbA1c ≥47.5 mmol/mol
Kapellas, Skilton et al. (2014) (XII)	CDC/AAP moderate periodontitis[b]	138 (77/61) Mean: 40 Range: ≥18	15.1%[a] for SR	–	–	SR: -Q
Kapellas, Maple-Brown et al. (2014) (XII)	CDC/AAP moderate and severe periodontitis[b]	271 (156/115) Mean: 39 Range: ≥18	15.1%[a]	39 (16/23) Mean: 36 Range: ≥18	0%	CM/SR -Q
LaMonte et al. (2014) (XIII)	Severe periodontal disease: Whole-mouth mean alveolar crestal height ≥3 mm or ≥2 sites ≥5 mm or ≥1 tooth loss due to periodontal disease	143 (0/143) Mean: 66 Range: 50–79	13.3%[a]	–	–	CM: -Fasting plasma glucose ≥100 mg/dl -Use of diabetes medication
Lee et al. (2014) (XIV)	Periodontal disease: CPI≥3	114 (n/a) Mean: n/a Range: ≥60	20.2%[a]	199 (n/a) Mean: n/a Range: ≥60	7.5%[a]	CM: Fasting glucose ≥126 mg/dl
Linden, McClean, Young, Evans, and Kee (2008) (XV)	CDC/AAP moderate and severe periodontitis[b]	591 (591/0) Mean: n/a Range: 58–72	5.6%[a]	–	–	SR: For those who reported a diabetes diagnosis, or listed a medication that suggested diabetes management, their general medical practitioner (GMP) was contacted to validate the diagnosis, type of diabetes and its management
Naito et al. (2007) (XVI)	Severe periodontitis: CPI = 4	17 (n/a) Mean: n/a Range: 22–59	11.8%[a]	–	–	CM: -Fasting plasma glucose ≥126 mg/dl and HbA1c ≥6.5%

(Continues)

TABLE 1 (Continued)

Author, year (ID)	Periodontitis case definitions	With periodontitis N = 29,594 Participants (M/F) Age (mean, range)	With periodontitis N = 29,594 Diabetes prevalence	Without periodontitis N = 53,746 Participants M/F Age (mean, range)	Without periodontitis N = 53,746 Diabetes prevalence	Type of diabetes assessment in the study
Nesse et al. (2010) (XVII)	Periodontitis: CPITN ≥3	888 (375/513) Mean: 45 Range: ≥18	5.2%[a]	320 (141/179) Mean: 33 Range: ≥18	1.6%[a]	SR: -Q
Park, Park, and Ko (2014) (XVIII)	Periodontal treatment needs: CPI ≥3	4,692 (2,531/2,161) Mean: n/a Range: 19–95	11.9%[a]	15,537 (6,114/9,423) Mean: n/a Range: 19–95	7.7%[a]	CM: -Fasting blood sugar ≥126 mg/dl -Use of antidiabetic medications
Soory (2007) (XIX)	Moderate periodontal disease: proportion of root length supported by bone of up to third Severe periodontal disease: proportion of root length supported by bone less than a half	87 (n/a) Mean: n/a Range: 20–75	6.9%[a]	–	–	SR: -Q
Susin, Wagner, Haas, Oppermann, and Albandar (2015) (XX)	Periodontitis: ≥30% of teeth with periodontal attachment loss ≥5 mm	376 (n/a) Mean: n/a Range: 18–65	9.6%[a]	828 (n/a) Mean n/a Range: 18–65	1.9%[a]	SR: -INT
Torrungruang et al. (2005) (XXI)	Mild periodontitis: Mean CAL <2.5 mm Moderate: Mean CAL: 2.5–3.9 Severe: Mean CAL: ≥4.0 mm	1,387 (n/a) Mean: 54 Range: 50–73	17.7%[a]	–	–	CM/SR: -Fasting blood sugar ≥126 mg/dl or -Taking antidiabetic medications
Torrungruang et al. (2009) (XXII)	Periodontitis: ≥3 sites with PPD ≥5 mm	164 (133/31) Mean: 48 Range: 39–59	14.6%[a]	289 (205/840) Mean: 47 Range: 39–59	4.5%[a]	CM/SR: -Fasting blood sugar ≥126 mg/dl or -Taking antidiabetic drugs during the past 2 weeks
Tu, D'Aiuto, Lin, Chen, and Chien (2013) (XXIII)	Periodontal disease: A tooth with combination of: -Tooth mobility -Gingival inflammation -Periodontal pocketing	10,401 (n/a) Mean: n/a Range: 14–94	20%[a]	23,339 (n/a) Mean: n/a Range: 14–94	13.7%[a]	CM: -Fasting glucose ≥126 mg/dl -Taking medication for diabetes
Rivas-Tumanyan, Campos, Zevallos, and Joshipura (2013) (XXIV)	CDC/AAP severe periodontitis[b]	43 (33/10) Mean: 77 Range: ≥70	36%	–	–	SR: -INT

(Continues)

TABLE 1 (Continued)

Author, year (ID)	Periodontitis case definitions	With periodontitis N = 29,594		Without periodontitis N = 53,746		Type of diabetes assessment in the study
		Participants (M/F) Age (mean, range)	Diabetes prevalence	Participants M/F Age (mean, range)	Diabetes prevalence	
Wick et al. (2013) (XXV)	Periodontitis: ≥4 teeth with PPD >4 mm, CAL ≥2 mm, radiographic evidence of bone loss	130 (73/57) Mean: 49 Range: n/a	10%[a]	46 (25/21) Mean: 47 Range: ≥70	6.5%[a]	SR: -Q
Zainoddin, Taib, Awang, Hassan, and Alam (2013) (XXVI)	Periodontitis: Mild: PPD 3–4 mm, moderate if PPD 5–6 mm, severe for PPD >6 mm	177 (n/a) Mean: n/a Range: 17–79	5.6%[a]	193 (n/a) Mean: n/a Range: 17–79	1.0%[a]	SR: -DR
Ziukaite, Slot, Cobb, Coucke, and Van der Weijden (2017) (XVII)	Minor: at all affected teeth, bone loss >1/3 of the root length or attachment loss ≤3 mm, Moderate: bone loss >1/3 and ≤1/2 of the root length or attachment loss 4–5 mm, Severe: bone loss >1/2 of the root length or attachment loss ≥6 mm	5,375 (2,429/2,946) Mean: 50 Range: 35–94	3.7%[a]	–	–	SR: -Q

CAL, clinical attachment level; PPD, probing pocket depth; BOP, bleeding on probing; LOA, loss of attachment; CPI, Community Periodontal Index; CPITN, the Community Periodontal Index of Treatment Needs,
[a]Percentage calculated by the reviewer; M, males; F, females; CM, diabetes mellitus was diagnosed in a clinical setting; SR, information about diabetes was self-reported by means of: INT, interview; Q, questionnaire; DR, dental records; n/a, unknown; *N*, the total number; *n*, numbers of participants in the subgroups;
[b]Page RC, Eke PI. 2007 Case definitions for use in population-based surveillance of periodontitis. J Periodontol 78 (7 Suppl):1387–99.

TABLE 2 Diabetes prevalence among different (non) periodontitis groups and the overall prevalence of periodontitis from the studied populations (NA - not applicable)

Prevalence of diabetes among		*SD*	Range	#Studies	#People
Overall studied population	**10.8%**	**4.8**	**2.3; 36.0**	**27**	**83,340**
Type of diabetes assessment					
Clinically assessed	12.8%	3.5	3.5; 25.3	10	57,322
Self-reported	5.5%	2.5	3.2; 34.1	14	23,905
Clinically assessed/self-reported	16.3%	4.6	8.2; 22.7	3	2,113
Subjects with periodontitis	**13.1%**	**6.7**	**2.3; 36.0**	**27**	**29,594**
Type of diabetes assessment					
Clinically assessed	17.3%	4.0	7.7; 23.6	10	16,430
Self-reported	6.2%	4.0	2.3; 36.0	14	11,340
Clinically assessed/self-reported	18.2%	2.1	14.6; 22.7	3	1,824
Subjects without periodontitis	**9.6%**	**3.9**	**1.0; 20.5**	**15**	**53,746**
Type of diabetes assessment					
Clinically assessed	11.0%	3.1	2.9; 20.5	8	40,892
Self-reported	4.8%	1.7	1.0; 14.5	6	12,565
Clinically assessed/self-reported	4.5%	NA	NA	1	289
Prevalence of periodontitis					
Overall studied population	**27.0%**	**9.6**	**11.0; 73.9**	**15**	**73,663**

varied from 2.3% to 36% (Table 1). The overall weighted mean prevalence of diabetes within subjects with periodontitis was 13.1%. The prevalence was also assessed for the periodontal part of the population and the whole study population taken together. A weighted mean prevalence was calculated including four studies (I, X, XIII, XX) that had a "low" estimated risk of bias, which resulted in a prevalence of diabetes among subjects with periodontitis to be 10.8%.

The subanalysis with regard to the assessment of diabetes revealed the prevalence of 6.2% and 17.3% for self-reported and clinically assessed diabetes mellitus, respectively (Table 2, Table S4). Based on a subanalysis of geographical regions, the highest diabetes prevalence was observed in studies conducted in Asia (17.2%, *n* = 18,002) followed by South America (11.9%, *n* = 516) and North America (10.3%, *n* = 2,945). The lowest prevalence was observed in studies originating from Europe, which was 4.3% (*n* = 7,858) (Table S5).

Odds ratios (OR) with "random-effect" model from data of 16 studies were calculated for subject with periodontitis to have diabetes, which was 2.27 (95% CI [1.90;2.72]) (Figure S1). OR were also estimated for only self-reported and clinically assessed diabetes which varied from 2.92 to 1.82, respectively (Table 3). Odds ratio was calculated including three studies with a "low" estimated risk of bias, which resulted in 2.80 (2.02;3.87). The funnel plot (Figure S2) shows that almost all outcomes are located at the top of the funnel, which is suggestive for publication bias. Also from Table S4, it is evident that in most studies the prevalence of diabetes among participants without periodontitis is underestimated as compared to the national mean prevalence as reported by World Health Organization (2016).

Table 4 shows a summary of the factors used to establish the body of evidence according to GRADE (2014) and the risk magnitude. There is a moderate level of certainty that the odds of having diabetes among a periodontitis population as compared to a non-periodontitis population is weak to moderate. The magnitude of this observation is dependent on the approach in which diabetes was assessed being either self-reported or clinically measured.

Two of 20 included papers used the same definition regarding periodontitis classification and used the same method to assess diabetes. A dose–response relationship was observed when weighted mean prevalence of diabetes among subjects with different severity groups of periodontitis was calculated (see Table S8).

4 | DISCUSSION

The present review summarized the available body of dental and medical literature with respect to an important question that examines the periodontal disease–diabetes relationship from the reverse viewpoint of the more commonly asked question (what is the prevalence of periodontitis among patients with diabetes). The average prevalence of periodontitis was 27.0% among study populations (Table 2). This appears to be in line with what is reported throughout the world. Periodontitis in adults in Australia and Germany is prevalent by 25% (age: 35–54) and 34% (age: 30–39), respectively (Dye, 2012). In China, the prevalence of moderate periodontitis reported to be 24% within 1,728 adults (Zhang et al., 2014). These figures indicate that what is observed in the included studies is not biased towards periodontal disease. Three papers (selection ID's: IV, VIII, XII) however reported their findings from indigenous people. In all three original articles, authors mentioned that these groups have poorer oral health status, including periodontal condition as compared with non-indigenous counterparts. These three may have introduced bias in estimation of periodontitis prevalence among the whole studied population as extracted from 27 papers altogether.

TABLE 3 Odds ratios for subjects with periodontitis to have diabetes

Analysis	Number of comparisons included for OR calculation	Model used	OR	95% CI	*p*-Value	Heterogeneity		
						Tau^2	I^2	*p*-value
Overall	16	Random	2.27	1.90; 2.72	<.00001	0.05	74%	<.00001
Subgroup analysis (type of diabetes assessment):								
Self-reported	7	Random	2.92	2.00; 4.26	<.00001	0.10	47%	0.08
Clinically assessed	8	Random	1.82	1.55; 2.13	<.00001	0.02	60%	<.001

A "random-effect" analysis was performed as suggested by Higgins and Green (43). As a rough guide for assessing the possible magnitude of inconsistency across studies, I^2 statistic of 0%–40% was interpreted as not to be imperative, and above 40% moderate to considerable heterogeneity was supposed to be present.

TABLE 4 GRADE evidence profile and the odds ratios of having diabetes as a subject with periodontitis

Study design	Observational
Risk of bias	Low to high
Consistency	Fairly consistent
Precision	Precise
Directness	Generalizable
Publication bias	Likely
Body of evidence	Moderate
Magnitude of the risk[a]	Weak to moderate

[a]Magnitude of the prevalence and odds of having diabetes among a periodontitis population as compared to a non-periodontitis population considering the potential burden diabetes may bring to the periodontitis population.

The worldwide prevalence of diabetes mellitus as based on data from 83340 people irrespective of their periodontal status was 10.8%. This appears to be close to what is reported throughout the world with respect to diabetes occurrence. The International Diabetes Federation (IDF) (2015) reported the worldwide prevalence of diabetes in 2014 to be 8% within 20- to 79-year adults. The WHO (2016) published the global diabetes prevalence to be 9.2% for adults ≥18 years. This figure indicates that if the data derived from the included studies are skewed, this is only slightly so towards metabolic disease conditions.

The assessment of the publication bias is suggestive of a bias towards a relatively elevated prevalence of diabetes among subjects with periodontitis (online appendix Table S4). This is confirmed when the four studies with a "low" estimated risk of bias are considered which report a prevalence of diabetes of 9.9% (SD=2.9) among the periodontitis populations, a figure that is only slightly elevated as compared to the worldwide prevalence of 9.2% as reported by WHO (2016).

Several selected studies reported on the prevalence of diabetes mellitus among subjects without periodontitis, which was found to be 9.6%. The data of those studies that reported on non-periodontitis participants could be set against the data that concerned subjects with periodontitis. Based on this, the odds ratio for subjects with periodontitis to be diagnosed with diabetes was 2.27 (95% CI [1.90;2.72]). If this is set against the literature, comparable data are lacking. Although a very recent publication from the Netherlands has reported, the 2.2% prevalence of diabetes among non-professionally evaluated people without periodontitis (Beukers, van der Heijden, van Wijk, & Loos, 2017). Most studies concerning the relationship between diabetes–periodontitis report on the reverse outcome, that is the prevalence of periodontitis among patients with diabetes. From the literature over the past few decades (Chavarry, Vettore, Sansone, & Sheiham, 2009; Kinane & Chestnutt, 1997; Soskolne, 1998) and in the review by Taylor (2001), it is noted that the prevalence of diabetes increases the prevalence, incidence and severity of periodontitis. Borgnakke et al. (2013) suggested that periodontal disease adversely affects diabetes outcomes and that further longitudinal studies are warranted.

For the present review, the inclusion criteria for the method of classifying a participant as having diabetes were based on a clinical assessment, self-reported or both (Table S4). However, for example, a quarter (27.8%) of US individuals with diabetes is undiagnosed and therefore will not report having diabetes (Centers for Disease Control and Prevention, 2014, Eke et al., 2016). This introduces differences in the estimated prevalence of the included papers (see further discussion in Limitations (S1). The outcome of the paper indicates that the self-report of having been diagnosed with diabetes resulted in a diabetes prevalence of 6.2% among subjects with periodontitis. This seems a relative underestimation of diabetes prevalence when comparing it to the clinically assessed results (17.3%). In medical surveys, self-report data are commonly used to estimate the prevalence of health conditions and the use of preventive health services in a population. The validity of such data can however be questioned. For example, self-reports of chronic conditions were compared with health maintenance organization's medical records for 599 adults aged >21. Sensitivity was moderate (73%), and specificity was high (99.3%) for diabetes (Martin, Leff, Calonge, Garrett, & Nelson, 2000). In a randomly selected group (n = 2,037) of US residents (≥45 years), participants were asked whether they had diabetes. Medical records were abstracted and analysed against self-report of disease. This also showed high (>90%) specificity, but low sensitivity (66%) for diabetes (Okura, Urban, Mahoney, Jacobsen, & Rodeheffer, 2004). Jackson et al. (2014) investigated positive and

negative predictive values of self-reported diabetes. In addition, medical records were obtained and reviewed for documented treatment with antidiabetic medications or for physician diagnosis of diabetes supported by laboratory measurements of glucose. Their data show high positive predictive values of self-reported prevalent diabetes (91.8%) and a high negative predictive value (94.5%) when diabetes is not reported. Altogether, to be on the safe side future research in relation to metabolic status should preferably use clinically assessed diagnosis.

The large number of included studies allowed subanalyses by geographical regions in which the examined study population lived and the data were summarized by geographical region (Table S5). The highest prevalence of diabetes within populations of subjects with periodontitis was observed in studies conducted in Asia (17.2%, *n* = 18,002). Diabetic condition in these included studies was more frequently assessed clinically rather than by self-report. This prominence towards clinically measured could explain the relatively high level. The only reported prevalence in Australia was 22.7%. The results are however based on one convenience sample of indigenous Australian adults, which have poorer oral and general health than their non-indigenous counterparts (Gracey & King, 2009). It might explain the threefold higher diabetes value than is reported by WHO (2016) (6.6%). The lowest prevalence of diabetes was observed in the included studies from Europe, which was 4.3% as obtained evaluating in total 7,858 subjects. The prevalence is almost the same as reported by IDF (6.2%) (2014). All selected European studies presented data about self-reported diabetes. The lower prevalence based on what the participants report as compared to clinically measured might imply an underestimation (Table S4). As opposed to studies from other geographical regions, two of three European studies showed the prevalence of diabetes among subjects with periodontitis to be numerically lower than the national mean estimate (WHO, 2016). From Table S4, it is also evident that in most other studies the prevalence of diabetes among people without periodontitis is underestimated as compared to the national mean prevalence reported by WHO (2016), which will consequently inflate the observed risk.

Diabetes is usually diagnosed based on plasma glucose criteria, either the fasting plasma glucose or the 2-hr plasma glucose value after a 75-g oral glucose tolerance test (National Diabetes Information Clearinghouse, 2014). For epidemiological or population screening purposes (WHO, 1999), The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003) proposes to assess fasting or 2-hr values after 75-g oral glucose consumption. For clinical purposes, according to the National Institute of Diabetes and Digestive and Kidney Diseases and National Institutes of Health of United States, a level of 126 mg/dl or above, confirmed by repeating the test on another day, implies that a person has diabetes. As the results of the current systematic review could be taken into consideration while making clinical implications, it should be considered that although diagnostic criteria were rather consistent, heterogeneity was observed between diagnostic methods and references used. Recently, an International Expert Committee (International Expert Committee 2009) added the HbA1c (threshold ≥6.5%) as a third option to diagnose diabetes. One paper (XII) included in the current review assessed diabetes based on HbA1c values. It can be expected that in future studies presenting data on the prevalence of diabetes will also be based on the HbA1c test. It should be interesting to learn what this new test will bring with respect to the disease prevalence as compared to percentages assessed in epidemiological studies using fasting glucose or oral glucose tolerance test.

Several limitations concerning this systematic review were identified. One of the major limitations considers the inclusion criteria for the method of classifying a participant as having diabetes was based on a clinical assessment, self-reported or both. However, for example, a quarter (27.8%) of US individuals with diabetes is undiagnosed and therefore will not report having diabetes (Centers for Disease Control and Prevention, 2014, Eke et al., 2016). This introduces differences in the estimated prevalence of the included papers.

In order to summarize data from different geographical regions, it was chosen to present these by geographical region. The reader should however be aware that the reported studies do not capture the true prevalence of the certain geographic regions. For some regions of the world, a paucity of data exists and some studies have sampled from within small geographic regions, which are not representative for all of the people on a given continent. In order to establish the true prevalence in the future, many more studies using appropriate epidemiologic sampling techniques are needed to assess the prevalence in the majority of the countries and different geographical regions. The data from the present review however do clearly illustrate that geographical differences exist. The future guidelines for periodontal care in patients with diabetes should consider varying access to medical care amidst geographic areas. Details are presented in the Limitations S1. In addition, recommendations for future research are provided (Recommendations S1).

In conclusion, the worldwide prevalence and odds of having diabetes is higher within periodontitis populations compared to people without periodontitis. Self-reported diabetes underestimates the prevalence when compared to clinically assessed diabetes. The latter should be used in future dental research to avoid bias. Clear geographical differences in the prevalence were observed.

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AUTHORSHIP CONTRIBUTION

Laura Ziukaite, first author, contributed to the design, contributed to acquisition, analysis and interpretation, and drafted manuscript; Dagmar Else Slot contributed to the conception and design, contributed to acquisition, analysis and interpretation, and drafted manuscript; Fridus Van der Weijden, overall supervisor, contributed to conception and design, contributed to acquisition, analysis and interpretation, and critically revised manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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*Studies of the reference list that were selected for this review.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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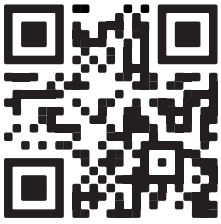
Chapter 2
Online appendices



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Chapter 3

The risk of tooth loss in patients with diabetes:

A systematic review and meta-analysis.

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REVIEW ARTICLE

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The risk of tooth loss in patients with diabetes: A systematic review and meta-analysis

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Abstract

Aim: 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.

Materials and 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.

KEYWORDS
diabetes mellitus, number of teeth, oral health, risk ratio, systematic review, tooth loss

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1 | 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.[7] The negative effects of elevated blood sugars on the immune system result in an increased susceptibility to infections.[8] The risk for development and progression of periodontitis is increased approximately threefold in DM patients as compared to non-diabetic individuals (non-DM).[9,10] Furthermore, DM is associated with increased severity of periodontal disease.[11] The increased risk of dental caries in DM patients can likely be explained by decreased salivary flow rates[12] and expanded levels of glucose in the saliva.[13] The American Diabetes Association and International Diabetes Federation have published DM care guidelines,[7,14] of which the main goal is prevention and treatment of DM complications, thereby optimizing quality of life (QoL).[14]

Periodontal pocket depth and clinical attachment loss are commonly utilized to define a patient with periodontitis.[15] 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.[1] A recent systematic review (SR) and meta-analysis assesses predictors of tooth loss, including DM, in periodontitis patients.[16] 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.

2 | METHODS AND MATERIALS

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 Ethical Committee by number 2021-71228.

2.1 | Focused question

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

- 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.

2.2 | 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 (L.P.M.W. and D.E.S.). 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

TABLE 1 Search terms used for PubMed-MEDLINE. The search strategy was customized according to the database being searched. The following strategy was used in the search: **{[<exposure>] AND [<outcome>]}**

{[<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]) OR number of teeth [MeSH Terms])]}

(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 hand-searched 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*.

2.3 | 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 (L.P.M.W. and D.E.S.). 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).
  - Diabetes mellitus or any other synonym, such as impaired glucose tolerance, glucose metabolism, glycaemic 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, L.P.M.W. and D.E.S.

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 diabetes 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, G.A.W., was consulted, whose judgement 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).

2.4 | Methodological quality assessment

Two reviewers (L.P.M.W. and D.E.S.) 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 modelled 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 judgements 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]

2.5 | 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 (L.P.M.W. and D.E.S.) utilizing a custom-designed standardized data extraction form. Disagreement between the reviewers was resolved through discussion and consensus. If disagreement persisted, a third reviewer (G.A.W.) was consulted; this judgement was decisive. Data extraction of all included studies having either an observational, cohort or case-controlled design was 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 were 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 were 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.

2.6 | Data analysis

2.6.1 | 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, gender and continent.
- Evaluable number of teeth.
- DM type: I or II.
- 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.

2.6.2 | Descriptive methods

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

2.6.3 | 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.[17] 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]

2.6.4 | Assessment of statistical heterogeneity

Statistically, heterogeneity was tested by the chi-square test and I^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 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 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.[28,29]

2.7 | Grading the body of evidence

Two reviewers (L.P.M.W. and D.E.S.) 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 (G.A.W.) was decisive.

3 | RESULTS

3.1 | 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 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 2015[38] 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.

3.2 | 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 III[40] to 12.131 in Study I.[42] The female gender 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 gender distribution (III). The population in Study II[43] is a specific ethnic group (Hispanics or Latinos). Studies originating from the following world continents are present: Europe (VII,[44] IX[45] and X[46]), North America (II,[43] IV,[47] and VIII[48]), Asia (I[42] and VI[49]) and South America (III[40] and V).[50] 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 IX[45] and X[46] were specifically selected from a central hospital or institute for metabolic diseases. For inclusion in the individual studies, criteria

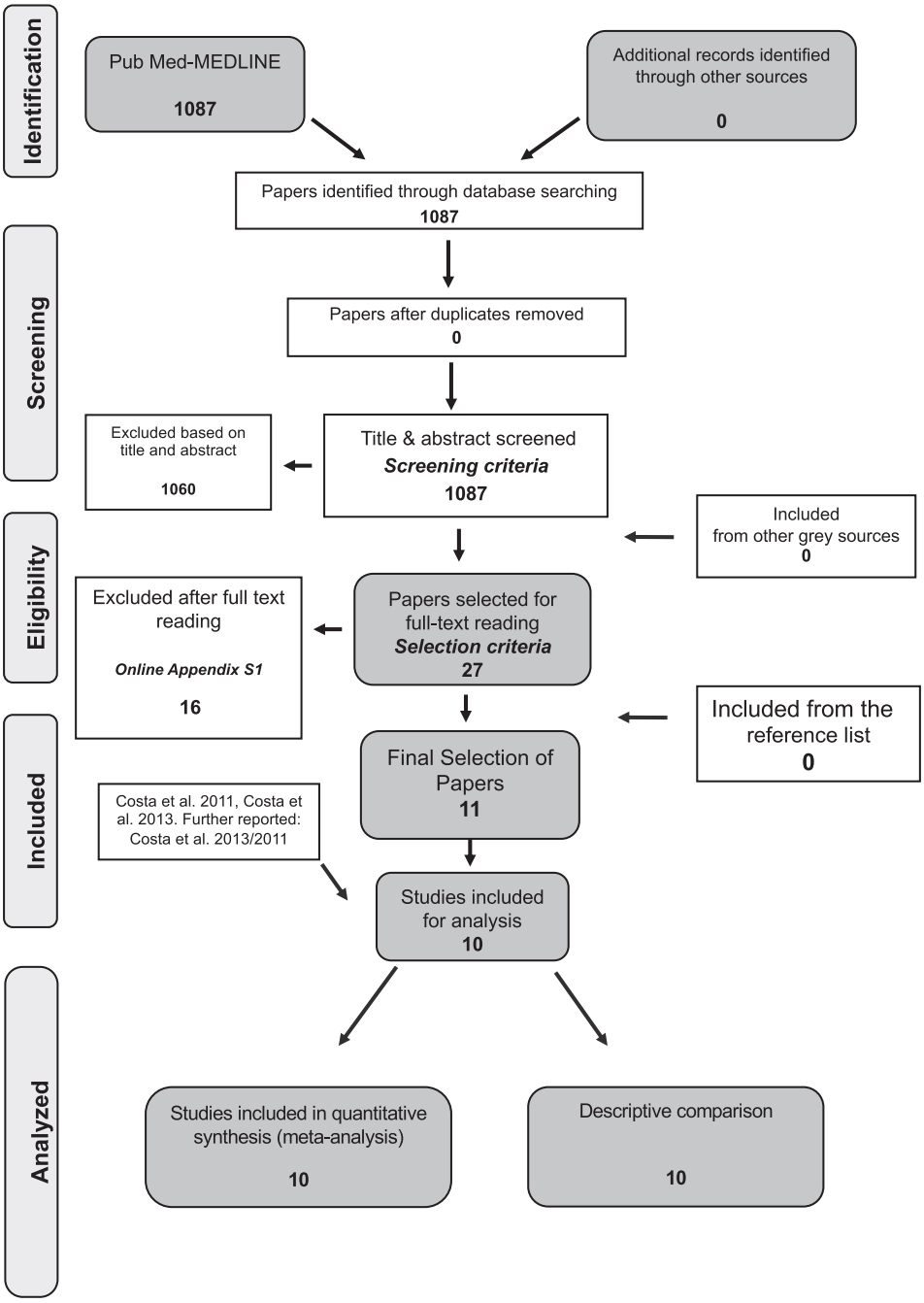

FIGURE 1 Search and selection results

and diagnoses were utilized regarding DM status: self-reported (IV[47]) and clinically assessed DM (I,[42] II,[43] III,[40] V,[50] VI,[49] VIII[48] and IX).[45] The clinical assessments were performed by different methods, such as fasting plasma glucose (FPG), glucose or HbA1c levels. Study VII[44] 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 VIII[48] 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 (II[43] and III[40]) report data on the DM group about well- and poorly controlled individuals. Smokers among non-DM individuals were separately analysed 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 (X[46]), insulin independence (IX[45]) and diagnosis of DM known beforehand or assessed on the spot.

3.3 | 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 (I,[42] II,[43] III,[40] IV,[47] V,[50] VII,[44] VIII[48] and X).[46]

3.4 | 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: II[43] and VII[44]; moderate for the majority of the studies: I,[42] III,[40] V,[50] VIII[48] and X[46]; and serious for the remaining three studies: IV,[47] VI[49] and IX.[45]

3.5 | Study results

From the included studies, the overall DM population consisted of 5699 patients and the non-DM controls of 23.579 individuals. The overall prevalence of DM in the included cross-sectional studies is 16.8%.

3.5.1 | 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.

3.5.2 | 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, $p < 0.0001$).

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 VII[44] presents usable data for a DM type I group, and therefore, no specific subgroup analysis could be performed.[17] 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

TABLE 2 Overview of the studies processed for data extraction

Selection ID **Authors, year,** **study design, country** **Risk of bias (Appendix S2)**	***N*** **Type of population**	**Gender (*N* males, *N* females)** **Mean age (SD)** **Range in years**	**Type of DM** **and type of assessment**	**#teeth in patients with DM** **Total *N* of teeth used for calculations**	**#teeth in people non-DM** **Total *N* of teeth used for calculations**
I: Shin et al. 2017 Cross-sectional Korea RoB: Moderate	Total: 12.131 ♦ DM: 1295 ♦ Non-DM: 10.836 ♦ Selected from KNHANES, a study periodically conducted by the Korea Centre for Disease Control and Prevention (KCDC), in 2012–2014.	Total ♂ 5342 ♦ ♀ 6789 ♦ Mean age: ? DM ♂:? ♀:? Mean age: ? Non-DM ♂:? ♀:? Mean age: ?	DM type II *Type of assessment: Prof-D*	Missing: 7356 ◊ Total teeth: 36.260 ◊ Patient level: 22,3 T+ ♦ 5,7 T- ◊ Based on 28 teeth ♦	Missing: 26.331 ◊ Total teeth: 303.408 ◊ Patient level: 25,6 T+ ♦ 2,4 T- ◊ Based on 28 teeth ♦
II: Greenblatt et al. 2016 Prospective cohort United States RoB: Low	Total: 9271 DM: 2792 ◊ Uncontrolled: 1324 Controlled: 1468 Non-DM: 6479 ♦ *Hispanic/Latino population; from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).*	Total ♂ 6089 ♦ ♀ 9043 ♦ Mean age: ? (18–74) DM ♂:? ♀:? Mean age: ? Non-DM ♂: ? ♀: ? Mean age: ?	DM type I/II *Type of assessment: Prof-D*	Missing: 10.140 ◊ Total teeth: 78.176 ◊ Patient level: 24,4 T+ ◊ 3,6 T- ◊ Based on 28 teeth ♦ Uncontrolled Missing: 5296 ♦ Total teeth: 37.072 ♦ Patient level: 28 T+ ◊ 4 T- ♦ Controlled Missing: 4844 ♦ Total teeth: 41.104 ♦ Patient level: 27,7 T+ ◊ 3,3 T- ♦	Missing: 20.733 ◊ Total teeth: 181.412 ◊ Patient level: 24.8 T+ ◊ 3.2 T- ♦ Based on 28 teeth ♦

(Continues)

TABLE 2 (Continued)

Selection ID Authors, year, study design, country Risk of bias (Appendix S2)	*N* Type of population	Gender (*N* males, *N* females) Mean age (SD) Range in years	Type of DM and type of assessment	#teeth in patients with DM Total *N* of teeth used for calculations	#teeth in people non-DM Total *N* of teeth used for calculations
III: Costa et al. 2013/2011 Case-controlled Brazil RoB: Moderate	Total: 92 ♦ DM: 46 ◊ Poor control: 23 ♦ Well control: 23 ♦ Non-DM: 46 ♦ Cohort undergoing PMT	Total ♂: 40 ♀: 52 Mean age: ? (22–71) DM ♂ 20 ♀ 26 Mean age: ? Poor control: ♂ 10 ♀ 13 Well control: ♂ 10 ♀ 13 Non-DM ♂ 20 ♀ 26 Mean age: ?	DM type II *Type of assessment: Prof-D*	Missing: 225 ◊ Total teeth: 1288 ◊ Patient level: 23,1 T+ ◊ 4,9 T- ◊ Based on 28 teeth ♦ Well-controlled Missing: 96 ◊ Total teeth: 644 ◊ Patient level: 23,8 T+ ◊ 4,2 T- ◊ Poorly controlled Missing: 129 ◊ Total teeth: 644 ◊ Patient level: 22,4 T+ ◊ 5,6 T- ◊	Missing: 183 ◊ Total teeth: 1288 ◊ Patient level: 24 T+ ◊ 4 T- ◊ Based on 28 teeth ♦
IV: Patel *et al.* 2013 Cross-sectional United States RoB: Serious	Total: 2055 ♦ DM: 384 ♦ Non-DM: 1671 ♦ *General population from the NHANES sample*	Total ♂ 992 ♦ ♀ 1063 ♦ Mean age: ? DM ♂: ? ♀: ? Mean age: ? Non-DM ♂: ? ♀: ? Mean age: ?	DM type I/II *Type of assessment: Self-R*	Missing: 3763 ◊ Total teeth: 10.752 ◊ Patient level: 18,2 T+ ◊ 9,8 T- ♦ Based on 28 teeth ♦	Missing: 11.196 ◊ Total teeth: 46.788 ◊ Patient level: 21,3 T+ ◊ 6,7 T -♦ Based on 28 teeth ♦
V: Botero et al. 2012 Cross-sectional Colombia RoB: Moderate	Total: 124 ◊ With DM: 65 ♦ Selected from the Hospital Universitario San Vicente de Paul (Medellin, Colombia) Non-DM: 59 ◊ Selected from the School of Dentistry at the Universidad del Valle	Total ♂: 67 ◊ ♀: 57 ◊ Mean age: ? DM ♂: 45 ♦ ♀: 20 ♦ Mean age: 57,4 ◊ Non-DM ♂: 22 ◊ ♀: 37 ◊ Mean age: 44,1 ◊	DM type I/II *Type of assessment: Prof-D*	Missing: 481 ◊ Total teeth: 1820 ◊ Patient level: 20,6 T+ ◊ 7,4 T- ◊ Based on 28 teeth ♦	Missing: 112 ◊ Total teeth: 1652 ◊ Patient level: 26.1 T+ ◊ 1.9 T- ◊ Based on 28 teeth ♦

(Continues)

TABLE 2 (Continued)

Selection ID Authors, year, study design, country Risk of bias (Appendix S2)	*N* Type of population	Gender (*N* males, *N* females) Mean age (SD) Range in years	Type of DM and type of assessment	#teeth in patients with DM Total *N* of teeth used for calculations	#teeth in people non-DM Total *N* of teeth used for calculations
VI: Sensorn et al. 2012 Cross-sectional Thailand RoB: Serious	Total: 605 ♦ DM: 379 ♦ Non-DM: 226 ♦ *General population living in Nachaluay district, Ubonratchathani, Thailand.*	Total ♂ 130 ◊ ♀ 475 ◊ Mean age: ? (20–86) ♦ DM ♂: 72 ♦ ♀: 307 ♦ Mean age: 54,7 ♦ Non-DM ♂: 58 ♦ ♀: 168 ♦ Mean age: 43,6 ♦	DM type I/II *Type of assessment: Prof-D*	Missing: 2414 ◊ Total teeth: 12.128 ◊ Patient level: 25,63 T+ ◊ 6,37 T- ◊ Based on 32 teeth ♦	Missing: 694◊ Total teeth: 7232◊ Patient level: 28,93 T+ ◊ 3,07 T- ◊ Based on 32 teeth ♦
VII: Kaur et al. 2009 Cross-sectional Germany RoB: Low	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*	Total ♂: 2055 ◊ ♀: 2233 ◊ Mean age: ? DM ♂: 180 ◊ ♀: 147 ◊ Mean age: 52,5 ◊ Type I ♂: 76 ♦ ♀: 69 ◊ Mean age: 37,4 ♦ Type II ♂: 104 ♦ ♀: 78 ◊ Mean age; 64,5 ♦ Non-DM ♂: 1875 ◊ ♀: 2086 ◊ Mean age: 46,8 ◊	DM type I/II (data are presented per type) *Type of assessment: T1DM Prof-D* *SHIP/T2DM: Self-R* *Type of assessment: Self-R (T1DM) and/or Prof-D (T2DM)*	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- ♦	Missing: 282.184◊ Total teeth: 110.908 ◊ Patient level: Non-DM (compared DMI&II) 19,9 T+ ◊ 8,1 T -◊ Based on 28 teeth ♦ Non-DM (compared DM I) Missing: 13.764 ◊ Total teeth ever: 74.116◊ Patient level: 22,8 present teeth ◊ 5,2 missing teeth ♦ Non-DM (compared DM II) Missing: 14.454◊ Total teeth: 36.792◊ Patient level: 17,0 T+ ◊ 11,0 T- ♦
VIII: Patiño-Marín et al. 2008 Cross-sectional Mexico RoB: Moderate	Total: 70 ◊ DM: 35 ◊ Non-DM: 35 ◊ *General population in Mexico.*	Total ♂: 33 ◊ ♀: 46 ◊ Mean age: ? DM ♂: 14 ◊ ♀: 21 ♦ Mean age: 45 ♦ Non-DM ♂: 19 ◊ ♀: 25 ♦ Mean age: 42 ♦	DM type II *Type of assessment: Prof-D*	Missing: 200 ◊ Total teeth: 980 ◊ Patient level: 22,3 T+ ◊ 5,7 T- ♦ Based on 28 teeth ♦	Missing: 123 ◊ Total teeth: 980 ◊ Patient level: 24,5 T+ ◊ 3,5 T- ♦ Based on 28 teeth ♦

(Continues)

TABLE 2 (Continued)

Selection ID Authors, year, study design, country Risk of bias (Appendix S2)	*N* Type of population	Gender (*N* males, *N* females) Mean age (SD) Range in years	Type of DM and type of assessment	#teeth in patients with DM Total *N* of teeth used for calculations	#teeth in people non-DM Total *N* of teeth used for calculations
IX: Bacic et al. 1989 Cross-sectional Croatia RoB: Serious	Total: 411 ◊ DM: 222 ♦ Insulin dependent (IDDM): 109 ♦ Non-insulin dependent (NIDDM): 113 ♦ *DM patients: selected from the Vuk Vrhovac Institute of Diabetes, Endocrinology and Metabolic Diseases in Zagreb referred from all parts of Croatia.* Non-DM: 189 ♦ *Non-DM patients: general population of Croatia during a survey on the prevalence of periodontal disease and caries in Croatia.*	Total ♂: 245 ◊ ♀: 166 ◊ Mean age: ? DM: ♂: 130 ♦ ♀: 92 ♦ Mean age: 49,6 ♦ Non-DM: ♂: 115 ♦ ♀: 74 ♦ Mean age: 43,9 ♦	DM type I/II *Type of assessment: Prof-D*	Missing: 2731 ◊ Total teeth: 7104 ◊ Patient level: 19,7 T+ ◊ 12,3 T- ♦ Based on 32 teeth ♦	Missing: 1833 ◊ Total teeth: 6048 ◊ Patient level: 22,3 T+ ◊ 9,7 T- ♦ Based on 32 teeth ♦
X: Falk et al. 1989 Cross-sectional Sweden RoB: Moderate	Total: 231 ◊ DM: 154 ◊ Long duration 82 (28,9 years) Short duration: 72 (5,2 years) *Selected from the Department of medicine at the central Hospital in Jönköping, Sweden.* Non-DM: 77 ♦ *selected from the county council's register of persons residing in the borough of Jonkoping.* *General population*	Total ♂: 112 ◊ ♀: 119 ◊ Mean age: ? DM ♂: 78 ◊ ♀: 76 ◊ Mean age: ? (20–70) ♦ Long duration ♂: 40 ♦ ♀: 42 ♦ Short duration ♂: 38 ♦ ♀: 34 ♦ Non-DM ♂ 34 ♀ 43 Mean age: ?	DM type I/II *Type of assessment:?*	Missing: 1007 ◊ Total teeth: 4312 ◊ Patient level: 21,4 T+ ◊ 6,6 T- ◊ Based on 28 teeth ♦ Long duration Missing: 467 ◊ Total teeth: 2296 ◊ Patient level: 22,3 T+ ♦ 5,7 T- ◊ Short duration Missing: 540 ◊ Total teeth: 2016 ◊ Patient level: 20,5 T+ ♦ 7,5 T- ◊	Missing: 416◊ Total teeth: 2156◊ Patient level: 22.6 T+ ♦ 5.4 T- ◊ Based on 28 teeth ♦

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-reported; 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.

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

Study ID	Bias due confounding	Bias in selection of participants into the study	Bias in classification of exposures	Bias due to departures from intended exposures	Bias due missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias	For details, see online appendix
I	Moderate	Low	Low	Moderate	Low	Low	Low	**Moderate**	S2-2
II	Low	Low	Low	Low	Low	Low	Low	**Low**	S2-3
III	Moderate	Moderate	Low	Low	Low	Low	Low	**Moderate**	S2-4
IV	Low	Low	Moderate	Serious	Moderate	Low	Low	**Serious**	S2-5
V	Moderate	Moderate	Moderate	Moderate	Low	Low	Low	**Moderate**	S2-6
VI	Low	Serious	Serious	Moderate	Low	Low	Low	**Serious**	S2-7
VII	Low	Low	Low	Low	Low	Low	Low	**Low**	S2-8
VIII	Moderate	Moderate	Low	Low	No information	Low	Low	**Moderate**	S2-9
IX	Serious	Moderate	Low	Moderate	Low	Low	Moderate	**Serious**	S2-10
X	Moderate	Low	Moderate	Moderate	Low	Low	Low	**Moderate**	S2-11

well-controlled DM patients were compared to non-DM individuals, as demonstrated by the RR: 1.03 with a 95% CI of 1.00 to 1.06 ($p = 0.04$). A higher risk of tooth loss in poorly controlled DM patients was found when 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% CIs, indicating that the overall analysis was robust.

3.5.3 | Statistical heterogeneity

Considerable heterogeneity was observed in the meta-analyses; for details, see Tables 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 I^2, 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 I^2 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 illustrates that the I^2 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.

3.6 | Publication bias

Testing for publication bias was possible for the overall analysis, which is presented in 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.

3.7 | Evidence profile

Table 7 presents a summary of the factors employed to establish the body of evidence profile according to GRADE (2014)[20] relative

TABLE 4 A 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
Total		6/10 have significant less teeth 0/10 no significant difference 4/0 do not specified	

?, unclear/not specified; 0, no difference; +, DM patients have significantly less teeth than non-DM.

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 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, Tables 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.

4 | DISCUSSION

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.[52,53] These are the two most common reasons for the endpoint parameter of tooth loss.

4.1 | 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 are retrieved from reported demographic data and presented as an interesting result.[54–56] Inclusion of these data may introduce a reporting bias that affects the conclusion drawn[57]; 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.[58] 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.

4.2 | Diabetes mellitus comorbidities

For this SR, only DM without reported comorbidities was considered. Papers on participants with other systemic diseases were excluded[59,60] 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, socio-economic status, family history of DM, geographical region and blood pressure.[61] The included papers did not adjust for these factors. Only in one paper (V[50]) 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

TABLE 5 Overview (sub) analysis overall and evaluable number of teeth (28/32)

	Included studies	Effect sizes				Heterogeneity		Funnel plot appendix	For details, see
		RR	Model	95% CI	*p*-Value	I^2 value	*p*-Value		
Overall	10 studies	1.63	Random	[1.33–2.00]	<0.00001	100%	<0.00001	S4	Figure 2
Number of teeth									
32 teeth	Bacic et al 1989 Sensorn et al 2012	1.51	Fixed	[1.45–1.58]	<0.00001	99%	<0.00001	S4	Figure 2
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	100%	<0.00001	S4	Figure 2

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 diabetics and periodontitis with the following factors: age, smoking habit and diabetic 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, gender, type of DM and type of assessment may interfere in the DM and tooth loss association.

4.3 | 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.[29,62] The consequences are that this may lead to overestimation of exposure as deducted based on the meta-analyses.[63] 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 either have not been published or have difficulties in being published in impact factor journals.[62]

4.4 | Type of diabetes

As prediabetes may be reversible,[64] data from these participants were not considered, as only one study (II[43]) was available. Gestational diabetes consists of high blood glucose only during pregnancy[65] and was consequently not analysed in the present review. Type I diabetes 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 diabetes cases.[66] Three of the included studies specifically focus on DM type II (I,[42] III[40] and VIII[48]). Only one paper (VII[44]) 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

TABLE 6 Overview sub-analysis: risk of bias, study design, world continent, DM type II and DM status

		Effect sizes				Heterogeneity			
	Included studies	RR	Model	95% CI	*p*-Value	I^2 value	*p*-Value	Funnel plot	For details, see
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	S3-1
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	[1.27–2.71]	0.001	98%	<0.00001	S4	S3-1
Serious	Patel et al. 2013 Bacic et al. 1989 Sensorn et al. 2012	1.48	Fixed	[1.45–1.52]	<0.00001	98%	<0.00001	S4	S3-1
Study design									
Cross-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	1.77	Random	[1.44–2.17]	<0.00001	99%	<0.00001	S4	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 Patiño Marín et al. 2008	1.22	Fixed	[1.20–1.24]	<0.00001	99%	<0.00001	S4	S3-3
Asia	Shin et al. 2017 Sensorn et al. 2012	2.30	Fixed	[2.25–2.36]	<0.00001	88%	0.004	S4	S3-3
South America	Costa et al. 2013/2011 Botero et al. 2012	2.27	Fixed	[2.00–2.58]	<0.00001	99%	<0.00001	S4	S3-3

(Continues)

TABLE 6 (Continued)

	Included studies	Effect sizes		95% CI	*p*-Value	Heterogeneity		Funnel plot	For details, see
		RR	Model			I^2 value	*p*-Value		
Solely diagnosed as DM type II									
Type II	Shin et al. 2017 Costa et al. 2011/2013 Kaur et al. 2009 Patino-Marin et al. 2008	1.56	Random	[1.02–2.39]	0.04	100%	<0.00001	S4	S3-4
Diabetic status									
Well-controlled vs. non-DM	Greenblatt et al. 2016 Costa et al. 2011/2013	1.03	Fixed	[1.00–1.06]	0.04	0%	0.88	S4	S3-5
Poorly controlled vs. non-DM	Greenblatt et al. 2016 Costa et al. 2011/2013	1.25	Fixed	[1.22–1.29]	<0.00001	23%	0.25	S4	S3-5
Poorly vs. well-controlled DM	Greenblatt et al. 2016 Costa et al. 2011/2013	1.21	Fixed	[1.17–1.26]	<0.00001	0%	0.41	S4	S3-5

non-DM individuals. Study VIII[48] 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 diabetes type II did not provide an explanation for the high level of heterogeneity. Only the subgroup analysis on diabetic status being either poorly or well-controlled revealed a low level of statistical heterogeneity (0%–23%). This could indicate that diabetic 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.

4.5 | 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.[65,67] 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.[68]

4.6 | 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.[69,70] 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 (IX[45] and VI[49]), 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% CI 1.29; 2.08] and [95% CI 1.45; 1.58], respectively; see Figure 2 and Table 5). 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 6 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 analysed 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 subanalysis 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.

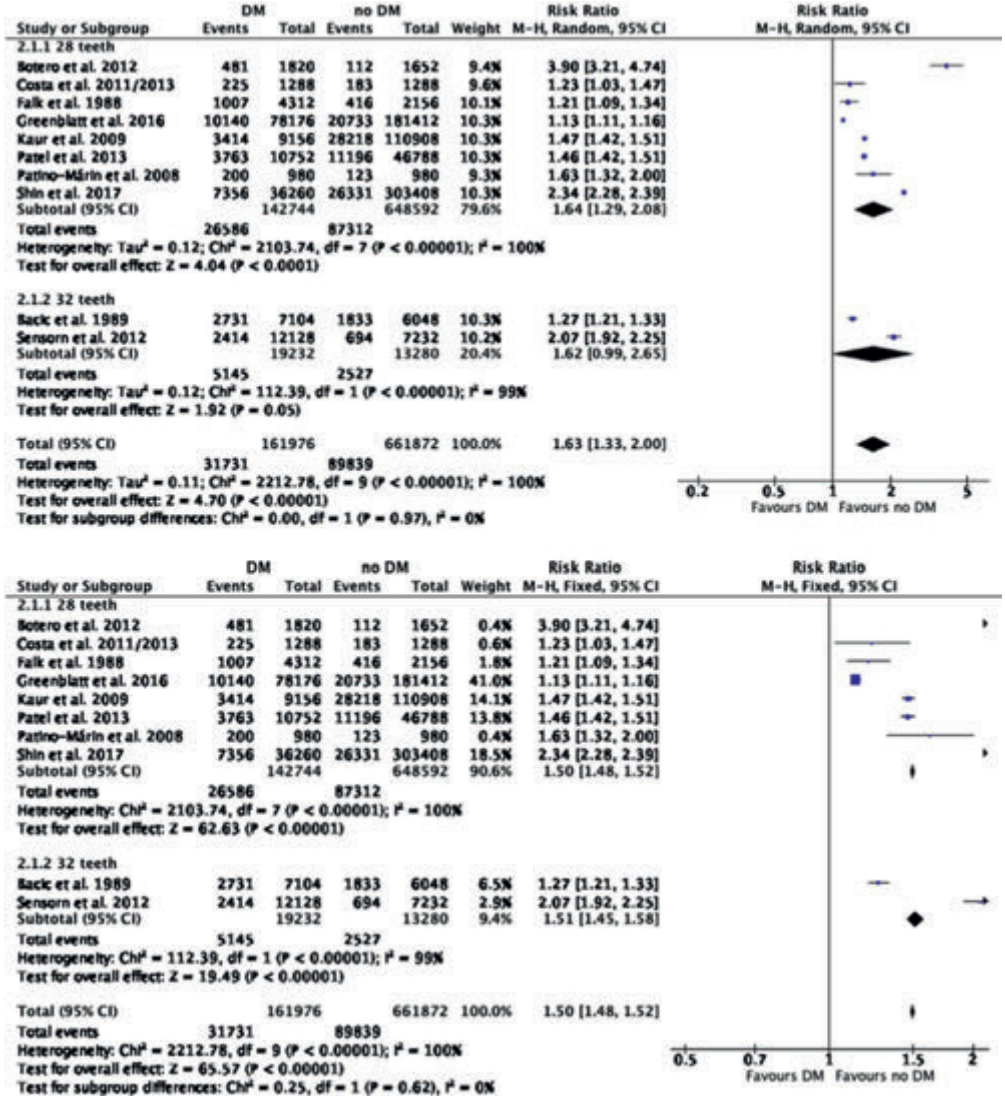

FIGURE 2 (2.1) Meta-analysis evaluating the effect of DM compared to non-DM on tooth loss using a random model: overall and evaluable number of teeth, 28/32 teeth. (2.2) Meta-analysis evaluating the effect of DM compared to non-DM on tooth loss using a fixed model: overall and evaluable number of teeth, 28/32 teeth

TABLE 7 GRADE 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, Tables 5 and 6 Online Appendix S3)	Rather precise
Reporting bias	Likely
Magnitude of the effect (Figure 2, Tables 5 and 6 Online Appendix S3)	Small
Strength of the recommendation based on the quality and body of evidence	Moderate
Direction of recommendation	**With respect to tooth loss, there is moderate certainty for a small risk for DM over non-DM**

4.7 | Geographical region

From the included cross-sectional studies, the prevalence of DM is 16.8%. The World Health Organization (WHO) published in 2016[71] the global DM prevalence as 9.2% for adults ≥18 years. This indicates that the data derived from the included studies are skewed towards 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 periodontitis[72] and that DM is found to be more prevalent compared to other ethnic groups.[73,74] 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 II[43] 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,[75] 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 United States[76] 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 geographical groups of North America, Europa, Japan and Oceania versus South America and Asia.[77] 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.

4.8 | Gender

Seven of the included papers feature more females than male participants, while DM type II is more common in males than females.[78] Females generally have a greater knowledge and more positive attitude than males towards oral health behaviour.[79] This is associated with a reduced risk for the progression and severity of periodontitis.[80] The skewed gender distribution towards females could cause underestimation of the outcome for this SR.

4.9 | 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.[81] 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.

4.10 | limitations & direction for further research

4.10.1 | Limitations

- The language restriction to English resulted in three potential studies that had to be excluded. Two were in Spanish,[82,83] and one was in Hungarian.[84] 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 tooth loss. None of the included studies provided details that could help discern what the indications for extraction had been.
- Factors such as differentiation between DM types I and II, type of assessment (self-report or professional), gender and age may have influenced the heterogeneity. This could not be further analysed 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 geographical regions, which may not represent the population of the continent.[23]

4.10.2 | Directions for further research

Despite these limitations, this SR is meaningful and indicates a higher level of tooth loss in DM patients. However, outcomes on age and smoking habits shall be considered in future research.

5 | 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.

6 | CLINICAL RELEVANCE

6.1 | Scientific rationale for the study

Diabetes mellitus (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 been systematically being reviewed whether DM is associated with a higher risk of tooth loss compared to non-DM individuals.

6.2 | Principal findings

Diabetes mellitus patients have a significantly higher risk of tooth loss than in non-DM individuals.

6.3 | Practical implications

Diabetes mellitus patients shall get attention on oral disease prevention by the dental care practitioners. They are at increased risk of tooth loss, which in particular applies to DM patients from Asia and South America.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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AUTHOR CONTRIBUTION

L.P.M.W. contributed to design, search and selection, analysis and interpretation and drafted the manuscript. L.Z. contributed to design, analysis and interpretation and critically revised the manuscript. G.A.W. contributed to conception and design, analysis and interpretation and critically revised the manuscript. E.W.P.B. contributed to analysis and interpretation and critically revised the manuscript. D.E.S. 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.*

ETHICAL APPROVAL

Ethical approval was not required. This study is registered at the ACTA University Ethical Committee by number 2021-71228.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources. The data that support the findings (the seven included studies) of this study are available from search databases PubMed/Medline or Cochrane-CENTRAL. These data were derived from resources available in original papers that are published in the public domain. Some first or corresponding authors of inculded papers were contacted for additional data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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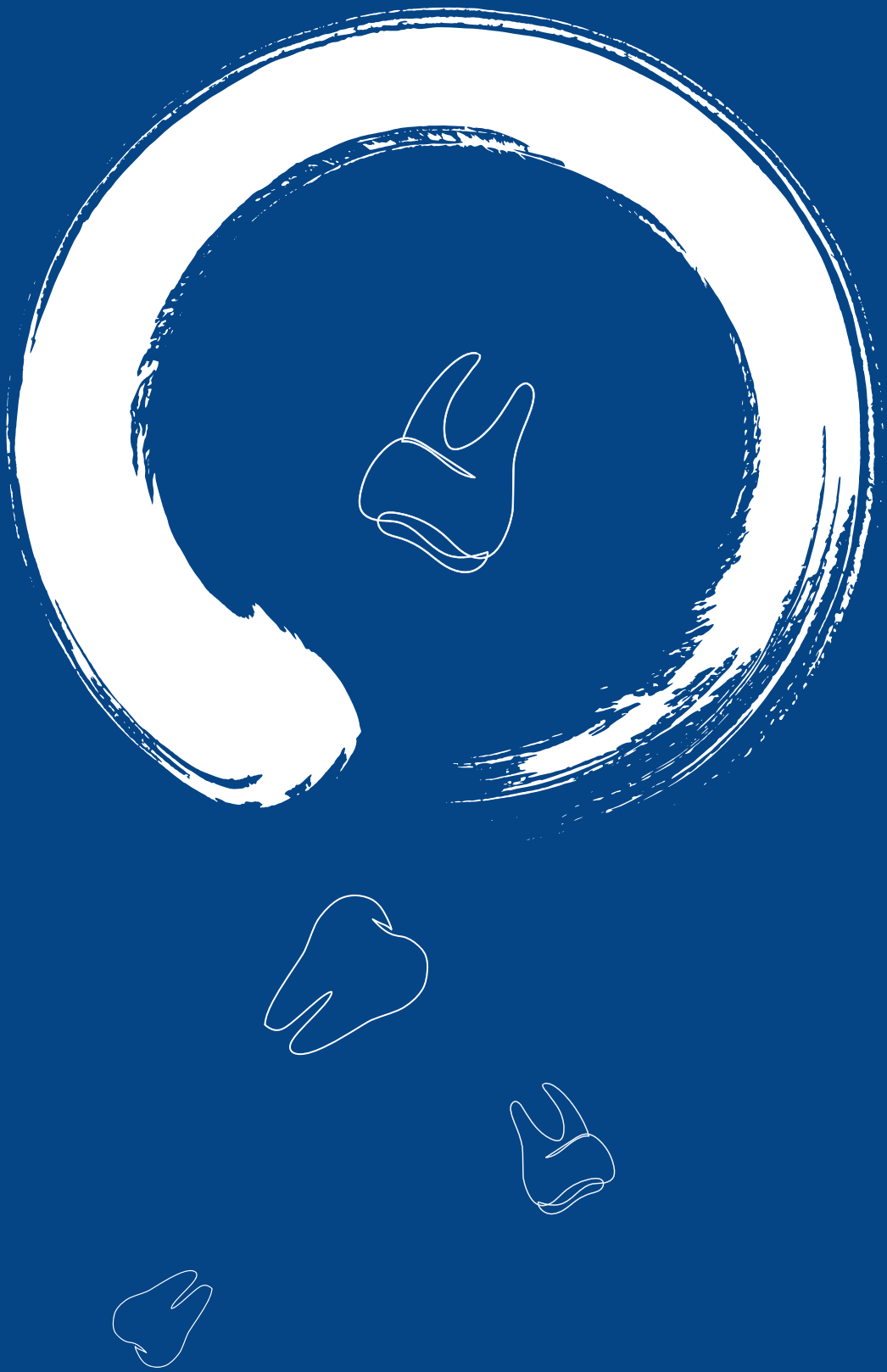
Chapter 3
Online appendices



Chapter 4

Edentulism among diabetic patients compared to non-diabetic controls:

A systematic review and meta-analysis.

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Abstract

Objective: This review determines the prevalence of edentulism among diabetic and nondiabetic patients based on a systematic evaluation of the available literature.

Methods: MEDLINE-PubMed, Cochrane-CENTRAL and EMBASE databases were comprehensively searched up to August 2022 to identify appropriate studies. The prevalence of edentulism was evaluated in populations with and without diabetes mellitus. Based on the extracted data a meta-analysis was performed.

Results: Independent screening of 449 unique titles and abstracts revealed 6 publications that met the eligibility criteria. Study size ranged from 293 to 15,943 participants. Data of all 6 studies were suitable for meta-analysis. Overall, 8.7% of the studied populations was edentulous. The weighted mean prevalence of edentulism among diabetic and non-diabetic patients was 14.1% and 7.5%, respectively. The overall odds ratio for diabetic patients to be edentulous as compared to non-diabetic patients was 2.49 (95%CI: [1.75;3.54], P<0.00001).

Conclusion: There is weak evidence that among individuals diagnosed with diabetes the prevalence of edentulism is higher than among non-diabetic patients.

Clinical relevance

Scientific rationale for the study

One of the main causes of edentulism, caries and periodontal disease, are supposedly more prevalent among diabetic patients. So far, a comprehensive assessment about the prevalence of edentulism among diabetic patients has not been performed.

Principle findings

The prevalence of edentulism among diabetic patients is significantly higher than among non-diabetic.

Practical implications

Tooth loss may occur because of various factors such as periodontitis or caries both of which are a sequel associated with diabetes mellitus. As the present review has established that diabetic status is significantly related to edentulism, diabetic patients should be cognizant that they are at a slightly higher risk of tooth loss.

Introduction

Diabetes mellitus is a metabolic syndrome that results in acute and chronic complications due to the absolute or relative lack of insulin (Ship 2003). Evidence exists supporting the association between periodontitis and diabetes mellitus (Borgnakke et al. 2013; Chávarry et al. 2009; Khader et al. 2006). This is a two-way association as has been described by the European Federation of Periodontology manifesto (2012).

Most of the studies that have evaluated diabetes's 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 (2005) 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 (Greenstein 2005). True endpoints (e.g., tooth retention or tooth loss) are more meaningful but require long-term and largescale epidemiological studies (Fleming 1992). Tooth loss can be easily assessed and precisely identified by both the patient and the clinician. Furthermore, tooth loss is considered a 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 (Beltrán-Aguilar et al. 2005; Gerritsen et al. 2010; Sheiham et al. 1997; Starr & Hall, 2010; U.S. Department of Health and Human Services, 2000). 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 (Greenstein 2005). 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 (Joshipura et al. 2000).

At present, the existing literature on the association between tooth loss and diabetes 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 diabetic patients compared to non-diabetic people.

Material and methods

This systematic review's protocol was developed in the planning stages following discussion between members of the research group. This study is registered at the ACTA University Ethical Committee by number 2022- 61102. The review was prepared according to the Meta-analysis of Observational Studies in Epidemiology guidelines (Stroup et al. 2000).

Focused question

The review question was formulated utilizing the population, exposure, comparison, outcomes and study (PECOS) framework as follows:
What is the prevalence of edentulism among diabetic patients compared to non-diabetic people, from observational studies?

Search strategy

The authors checked all systematic reviews 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, the Cochrane Central Register of Controlled Trials (CENTRAL), and Embase (the Excerpta Medica Database from Elsevier). The researchers searched the databases for studies conducted up to August 2022. 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:

{<diabetes> AND < edentulousness>}
{< diabetes > <("Glucose Metabolism Disorders"[Mesh]) OR ("Diabetes Mellitus"[Mesh]) OR (diabetes mellitus) OR (iddm) OR (niddm) OR (t2dm) OR (t1dm) OR (diabet*)>
AND
< edentulousness > <("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 (teethloss) OR (toothloss) 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 diabetic patients (specifically mentioned in the title or abstract)
- Studies with the pimary aim to investigate diabetic patients
- Studies of subjects who lived independently (not in nursing homes or other healthcare providing institutions)
- Studies that consisted of populations reporting to be:
    - People with diabetes (undefined, type I or type II)
    - People without diabetes
- Reported outcomes:
    - Prevalence or absolute numbers of subjects wearing complete dentures (in mandibula and maxilla) among diabetic patients and non-diabetic people
    - Prevalence or absolute numbers of complete edentulous subjects among diabetic patients and non-diabetic 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, gender)
- Edentulism and diabetes mellitus 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. (2013) 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. (2001) and used by Hennequin-Hoenderdos et al. (2016).

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 diabetic patients compared to non-diabetic people. If the selected papers did not report the prevalence of edentulism but did report the number of diabetic patients and non-diabetic people who were edentulous, the prevalence was calculated by dividing the number of edentulous patients among the diabetic or non-diabetic group by the total number of diabetic patients or non-diabetic people (for the complete overview, see Table 3).

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 diabetic patients and non-diabetic people were extracted and calculated for each study. A weighted mean prevalence was calculated as a percentage using the SPSS 21.0 statistical package (SPSS Inc., Chicago, IL, USA). Studies were assigned weights based on their sample size so that the proportion of information each study contributed to the analysis was taken into account. It was determined a priori to perform sub-analyses for the assessment method of subjects' diabetes (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 (RevMan version 5.1 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The odds ratio (OR) was calculated for edentulousness among diabetic patients compared to those without diabetes and was interpreted according to Chen et al. (2010): 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 fixed-effects analysis was performed because if the number of studies is very small it is not always feasible to estimate the between-studies variance (tausquared) with any precision (Borenstein et al. 2010). In such a case, the fixed-effects model is the most viable option. The formal testing for publication bias as proposed by Sterne and Egger (2001) was performed if ≥ 10 studies could be included in the meta-analysis (Higgins and Green 2009).

Grading the body of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE), as used by the GRADE working group (2014), 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 1976 unique papers (see Figure 1). After screening by titles and abstracts, 42 papers were selected for full-text reading, of which 36 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, six papers 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 process
* For details see Online Appendix S3

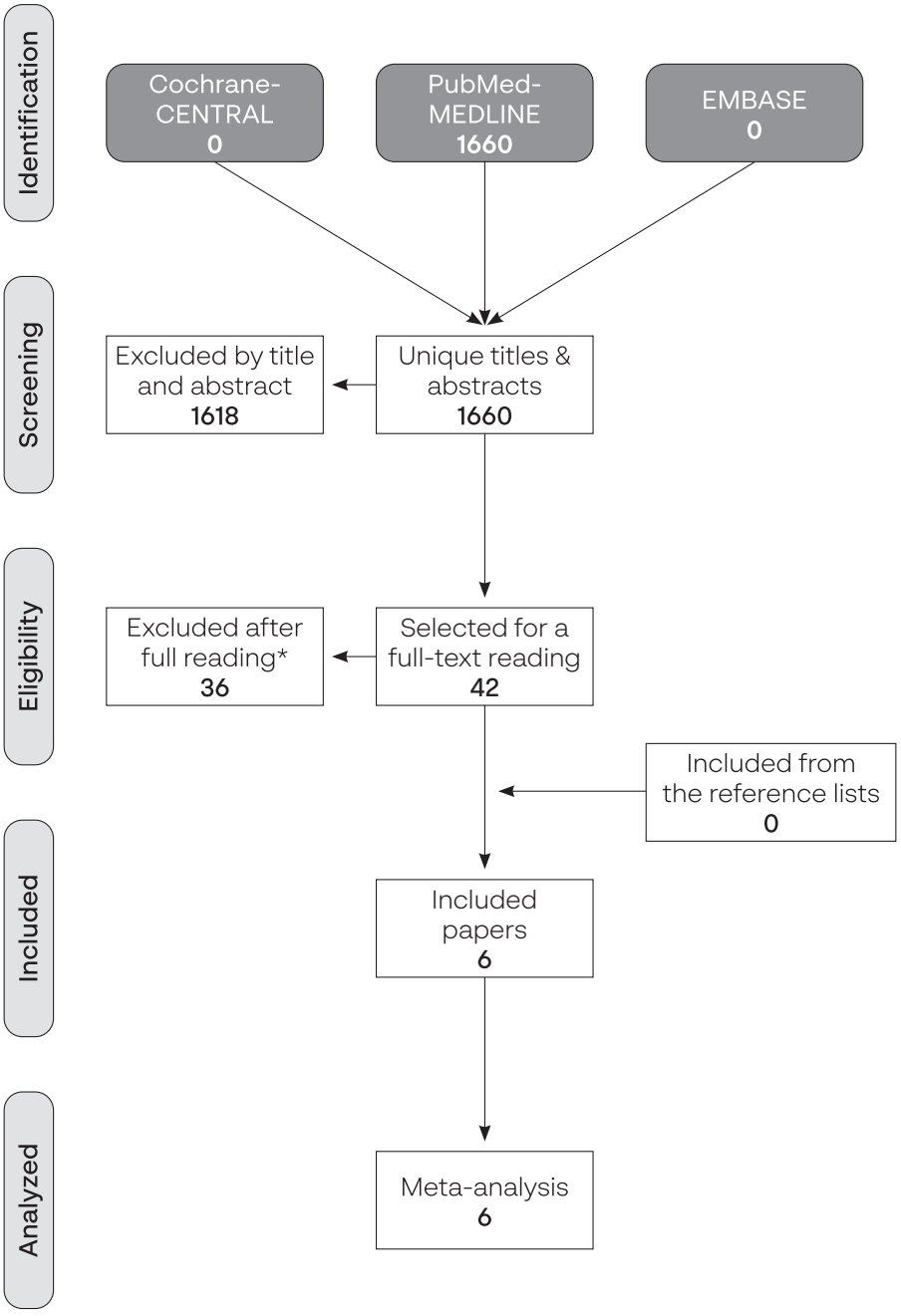


Table 2.
Details of included studies

Selection ID	Included studies Authors, year Country of research	Study design	N subjects Type of population	Gender Mean age (SD) Range in years	Type of diabetes Diagnosis of DM and E
(I)	Greenblatt et al. 2016 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)	Kowall et al. 2015 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
(III)	Mack et al. 2003 Germany	Cross-sectional (SHIP sample)	1793♦ General population	♂ ? ♀ ? ? (?) 55-79	Type DM: not specified DM: PD: - HbA1c E: CA
(IV)	Norlen et al. 1996 Sweden	Cross-sectiontal	483 Male population	♂ 483 ♀ 0 68 [68]	Type DM: not specified DM: PD - Blood
			Men born in 1914 in the city of Malmö in southern Sweden		concentration of glucose E: CA
(V)	Patel et al. 2013 United States	Cross-sectional of a cohort study (NHANES sample)	2508 General population	♂ 1215 ♀1293 ? (?) 50+	Type DM: DM1, DM2 DM: SR - Q E: CA
(VI)	Xie et al. 1999 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

Assessment of heterogeneity

Extracted data regarding the study designs, characteristics of the study populations, and the diagnostic methods of diabetes mellitus 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 (II, III, IV, VI) and two in North America (I, V).

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 gender distribution of the studied population as one study (V) included participants over 50 years of age, another (IV) included only men born in 1914 in the city of Malmö in Sweden, and another study from Finland (VI) investigated elderly people living at home. Three papers presented data from national surveys: the National Health and Nutrition Examination Survey in the United States (V) and the Study of Health in Pomerania in Germany (II: SHIP-Trend, III: SHIP).

Diagnosis of edentulism and diabetes mellitus

All included papers assessed edentulism clinically. Three papers (I, III, IV) presented data where diabetes mellitus was diagnosed professionally and two (V, VI) presented data where diabetes was self-reported, either through a medical questionnaire (V) or from dental or medical records (VI). The diabetes mellitus in one study (II) was based on both professional assessment and self-reports.

Methodological quality assessment

According to the modified NOS criteria for cross-sectional studies (Herzog et al. 2013), four studies (I, II, III, V) were considered to have a low risk of bias, two studies (IV, VI) had a moderate risk, and none had a high risk (Online Appendix S3).

Data analyses

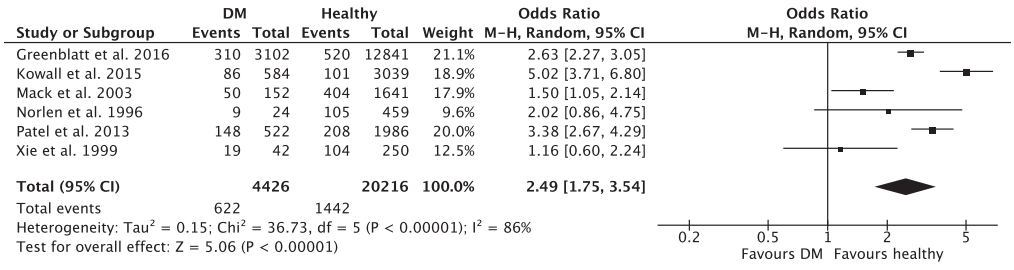
The data extraction revealed that the six studies involved a total of 2,136 edentulous cases. The range of prevalence of edentulism varied from 3.3% to 45% (see Online Appendix S4). The prevalence of edentulism among the whole study population was 8.7%. The overall weighted mean prevalence of edentulism was 14.1% among diabetic patients and 7.5% among non-diabetic people. The sub-analysis revealed a prevalence of edentulism of 19.7% and 7.7% for self-reported and clinically assessed diabetes, respectively. Based on the geographical region, edentulism prevalence was 14.2% for Europe and 6.8% for North America (see Table 3). The OR calculated with a random-effects model for diabetes mellitus patients to be edentulous was 2.49 (1.75; 3.54) based on the data of the six studies (see Figure 2).

ORs were also estimated for self-reported or professionally diagnosed diabetes and for different geographical regions, which showed a range of 2.10–2.92 (see Table 4).

Table 3.
Edentulism prevalence (total population and different sub-groups)

Edentulism prevalence	Edentulism (Clinically assessed)
Whole studied population	8.7%
Among subjects without diabetes	7.5%
Among subjects **with** diabetes	14.1%
Based on the diabetes mellitus assessment:	
Self-report	19.7%
Professionally diagnosed	7.7%
Based on geographical region:	
Europe	14.2%
North America	6.8%

Figure 2.
Meta-analysis 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 I2 value of 0–40% was interpreted as non-imperative, and moderate to considerable heterogeneity was assumed to be present for values above 40%

Table 4.
Odd ratios for diabetic patients to be edentulous

Analysis	Number of studies included for OR calculation calculation	Model	OR	95% CI	OR p-value	Heterogeneity I^2	Heterogeneity p-value
Overall	6	Random	2.49	1.75; 3.54	<0.00001	86%	<0.00001
Sub analysis how diabetes was measured							
Self-reported	2	Fixed	2.92	2.33; 3.65	<0.00001	89%	<0.003
Professionally diagnosed	3	Fixed	2.39	2.09; 2.73	<0.00001	76%	<0.002
Sub analysis per geographical region							
Europe	4	Random	2.10	0.95; 4.63	0.07	91%	<0.00001
North-America	2	Fixed	2.82	2.49; 3.20	<0.00001	68%	<0.00001

Grading the body of evidence

Table 5 summarizes the various factors used to rate the quality of evidence and strength of recommendations according to the GRADE working group (2014). There was a moderate level of certainty that the magnitude of the OR of being edentulous among a diabetic population as compared to a non-diabetic population is small.

Table 5.

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	In majority based on	Being edentulous
Study design	Table 2	Observational
# Studies	Figure 1, table 2	6
# Comparisons	Figure 1, table 2	6
Risk of Bias	Appendix S1, S3	Low to Moderate
Consistency	Table 2, 3, 4, Appendix S4	Rather inconsistent
Directness	Table 2	Rather generalizable
Precision	Table 3, 4	Precise
Reporting Bias	text	Possible
Magnitude of the odds ratio	Table 4	Small
Certainty	Table 2, 3, 4	Moderate

Discussion

The loss of teeth is considered the true endpoint for oral diseases; however, the majority of studies concerning the association between diabetes mellitus 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 (Elias & Sheiham 1998). A considerable body of literature has covered the link between diabetes mellitus and periodontal diseases (Borgnakke et al. 2013; Bullon et al. 2014; Chávarry et al. 2009; Khader et al., 2006; Simpson et al. 2015). The literature also demonstrates that the glucose content of gingival fluid is significantly elevated among diabetic patients compared to controls (e.g., Ficara et al. 1974), 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 periodontitisassociated bacteria in the dental biofilm (Rüdiger et al. 2002). 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 plaque formation before and after treatment in periodontitis patients suggests that the number of bacteria in the saliva also plays a role (Dahan et al. 2004). Diabetes 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 diabetic patients (Borg Andersson et al. 1998; Insuela et al. 2019; Singh et al. 2014). Thus, diabetes mellitus may exacerbate periodontal destruction and dental caries, causing the subsequent loss of affected teeth (Aida et al. 2006; Chestnutt et al. 2000). Consequently, edentulous patients are found to be at higher risk for poor nutrition (Felton 2009; Naka et al. 2014; Ritchie et al. 2002), which increases the risk of diabetes (Schulze et al. 2004). Furthermore, it has been demonstrated with moderate certainty that diabetic patients have a slightly higher risk of tooth loss that is nonetheless significant compared to those without diabetes (Weijdijk et al. 2021). 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 (Emami et al. 2013). This comprehensive review summarizes the available literature to determine the prevalence of edentulism among diabetic patients compared with non-diabetic 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 report (Petersen 2003) 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 diabetic patients and nondiabetic people whereas the WHO collected data from a much broader population. A recent review from Emami et al. (2013) 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 (Müller et al. 2006). 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 (Jingarwar et al. 2014; Patel 2012).

Diabetes diagnosis and control

The authors of one of the included studies (II) categorized participants according to their diabetes status in the following groups: normal glucose tolerance, pre-diabetes, newly detected type 2 diabetes mellitus, known type 2 diabetes mellitus with HbA1c < 7.0%, and known type 2 diabetes mellitus with HbA1c ≥ 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 diabetes: they found no increased prevalence of edentulism in well-controlled diabetes but did find an association between edentulism and poorly controlled diabetes.

Sub-group analysis was performed according to the diabetes assessment method (selfreported 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 diabetes (see Table 3). 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, II, III, V) 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 diabetic status. Study I collected and reported data regarding the number of diseases but did not specify them. A paper from Sweden (IV) investigated how males perceived their general health. Another paper (VI) reported data on heart failure and hypertension. However, it is likely that diabetic patients and non-diabetics 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 diabetic patients have a higher likelihood of edentulism than non-diabetic people.
To ensure the highest level of accuracy possible, only studies that specifically investigated the prevalence of edentulism among diabetic patients were included in this review.

Publication bias
Researchers have considered selective outcome reporting to be a major problem deserving of substantially more attention than it currently receives (Tannock 1996). 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) (Ghersi 2006). 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 diabetes 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, gender, 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 diabetes) now exists, causative evidence is still lacking. Researchers acknowledged that the gaps in our knowledge remain large (Linden GJ, Hersberg MC 2013). Treating periodontal disease while addressing other modifiable risk factors such as smoking, diabetes 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 paper (Tonetti et al. 2017) 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 diabetes. 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 take into account the specific needs to effectively support oral health as one of the fundamental components of general health (United Nations 2011) 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 (Glick et al., 2016; Lee, Watt, Williams & Giannobile, 2017). 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 diabetic patients compared to non-diabetic people is significant, but the odds ratio is estimated to be small.

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Conflict of interest
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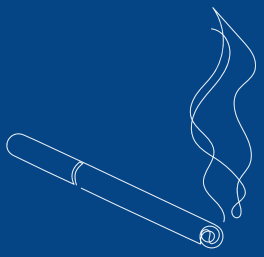
Chapter 4
Online appendices



Chapter 5

Family history of periodontal disease and prevalence of smoking status among adult periodontitis patients:
a cross-sectional study.

Ziukaite L, Slot DE, Loos BG, Coucke W, Van der Weijden GA.

Int J Dent Hyg. 2017 Nov;15(4):e28-e34.

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Family history of periodontal disease and prevalence of smoking status among adult periodontitis patients: a cross-sectional study

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Abstract: *Objectives:* What is the family history of periodontal disease and the prevalence of smoking status among patients with professionally diagnosed periodontitis? Are these factors related to extent and severity of periodontitis? *Methods:* Over a 10-year period, referred patients from a clinic for periodontology in the Netherlands were examined in a cross-sectional study. Patients received at the intake appointment a full-mouth periodontal examination. Data regarding family history of periodontitis and smoking status were recorded. *Results:* A total of 5375 adult periodontitis patients were included in this study sample with a mean age of 50 years. The prevalence of smoking was 34% and 37% of the subjects had at least one parent or sibling with periodontitis. The chance to have severe periodontitis was higher if the patient was male, smoker or had a brother with periodontitis. Being male, smoker and having a parent with periodontitis were significantly associated with a larger extent of periodontitis. *Conclusions:* Within the investigated population familial aggregation, smoking status, age and gender are factors that were related to extent and severity of adult periodontitis.

Key words: family; periodontitis; prevalence; smoking

Introduction

Periodontitis is a ubiquitous and irreversible inflammatory condition and represents a significant public health burden. Severe periodontitis affects over 11% of adults, is a major cause of tooth loss impacting negatively upon speech, nutrition, quality of life and self-esteem, and has systemic inflammatory consequences (1). The onset and progression of this condition is determined by the complex relationship among bacteria, host, behaviour and environmental factors determining the disease as multicausal, which is influenced also by risk factors (2–4). There are factors within the mouth, systemic factors related to the host and external (environmental) factors that modulate the interaction by potentiating the tissue. The so-called risk factors, synonymously called as risk indicators, are subdivided into subject characteristics, social, systemic and genetic factors, tooth-level factors, microbial composition of dental plaque, and others to mention (5). In the presence of one or more of these factors, there is an increased probability for periodontal disease to occur (6).

A wealth of epidemiological, clinical and *in vitro* studies has emerged that have provided irrefutable evidence that smoking negatively impacts periodontal health and proposes mechanisms by which this may occur (4, 7).

The importance of smoking as a risk factor for periodontal disease is supported by consistent results across many studies, strength of the association, dose–response of the association, temporal sequence of smoking and periodontal disease, and biologic plausibility (8).

Decades ago, the aggregation of different forms of periodontitis within families was noticed. A high familial aggregation was observed within siblings and affected pedigree members, reaching to 40–50%, suggesting that genetic factors may be important in susceptibility to aggressive periodontitis (9). Literature about familial aggregation of periodontitis among patients with this condition is less common.

Publications about the prevalence of the risk indicators specifically evaluating a population of periodontitis patients that have been referred to a clinic specialized in periodontology for periodontal treatment are scarce. With the respect to existing knowledge about the impact of risk indicators on periodontitis, it is of interest to investigate to what extent periodontal patients are exposed to them and to study the relative contribution of those to periodontal destruction.

Thus, the aim of this study was to investigate the prevalence of smoking status and family aggregation in a referred population of adult periodontitis patients and also to explore whether these indicators are related to extent and severity of periodontitis.

Methods

The study was prepared according to reporting guidelines as presented in the STROBE and RECORD checklist concerning items that should be included in reports of observational studies (Appendix S1). Because the obtained data as described below were part of the routine examination of newly referred patients, no ethics approval was required for this study.

Dataset of the studied population

This cross-sectional cohort study was performed among a population referred to a practice limited to periodontology, in the city of Utrecht, the Netherlands. The data were prospectively collected from 2003 to 2014 from the patients' initial periodontal examination at their intake appointment. Consecutive subjects having both a diagnosis of periodontitis and a completed questionnaire were considered as eligible for the study. Based on this database, the prevalence of diabetes among this population has been reported separately in another paper (10). The metabolic state appeared not to be a confounding factor because it did not significantly contribute to extent and severity of periodontitis.

Questionnaire

The periodontist interviewed and completed a structured questionnaire concerning demographics (age and gender), smoking habits (duration, type of smoking, number of cigarettes, duration of quit smoking) and self-reported history of periodontitis in close family members (mother, father, brother, sister, child, partner).

Periodontal diagnosis

Full-mouth periodontal examinations were performed by the same trained and experienced periodontist. Clinical measurements included gingival recession, probing pocket depth and bleeding upon probing. These data in combination with a full set of dental radiographs were used to classify each patient according to the criteria as proposed by Van der Velden (11, 12), which expressed extent by number of affected teeth and severity of periodontitis based on bone loss or attachment loss (for details, see Appendix S2).

Data extraction

Data of patients who were diagnosed with adult periodontitis were extracted. Data regarding the degree of extent and severity of periodontitis and the information obtained from the questionnaire were collected. Based on the original periodontitis categories (11, 12), groups were dichotomized as follows: less (combined: mild and moderate) and more severe (severe), less (combined: incidental and localized) and more (combined: semi-generalized and generalized) extent for groupwise comparisons.

Data analysis

The ratio of the total number of periodontal patients to the number of periodontal patients with one of the recorded parameters (prevalence) was calculated. The relation between the prevalence of discontinuous risk indicators and of extent or severity was first assessed by means of contingency tables. For the continuous risk indicators, data were summarized by means of number of data, mean, standard deviation, minimum and maximum.

In a second step to test the hypotheses, confirmatory statistical analysis was performed by means of a generalized linear model using a logit link with each prevalence variable modelled as a binary outcome and each risk factor individually. If a relation was significant, groupwise comparisons were made between the groups of the discontinuous risk indicators and *P*-values were corrected for simultaneous hypothesis testing according to Tukey. The regression coefficient of the continuous variables was used as an indicator of the direction of the relation between the continuous variables and the prevalence factors.

In a third step, a stepwise multiple regression variable selection was made to find the subset of risk indicators that predict each prevalence variable the best.

The prevalence of smoking over time was assessed by means of a generalized linear model using the logit link, current smoking status as binary outcome variable and year of intake as continuous predictive variable.

Results

General results

Overall, the records of 5375 subjects with a complete data set were included in the study (Table 1). The mean age was 50 years (range: 35–94). The gender distribution was 54.7% females (n = 2946) and 45.3% males (n = 2429). While 34.4% of subjects were smokers, 36.5% and 29.1% were non-smokers and former smokers, respectively. Partner and mother were the most frequently reported family members having periodontal problems: 17.3% and 17.2%, respectively. Table 1 also shows that 13.9% of patients had a father, 13.3% a sister, 10.5% a brother and 4% a child with periodontal problems. Patients were aware mostly about their child's and partners' presence or absence of periodontal problems.

Table 1. **Subjects' characteristics and prevalence of self-reported risk indicators (smoking and familial aggregation of periodontitis)**

	N (%)
Number of subjects	5375
Age, mean years (SD)	50.3 (9.7)
Females	2946 (54.7)
Males	2429 (45.3)
Self-reported smoking status *n* (%)	
Smoker	1852 (34.4)
Non-smoker	1964 (36.5)
Former smoker	1559 (29.1)
Self-reported family history of periodontitis	
Father	
Yes	742 (13.9)
No	1597 (29.7)
?	3036 (56.4)
Mother	
Yes	922 (17.2)
No	1633 (30.4)
?	2820 (52.4)
Brother	
Yes	561 (10.5)
No	2130 (39.6)
?	1594 (29.7)
NA	1089 (20.2)
Sister	
Yes	711 (13.3)
No	2168 (40.3)
?	1406 (26.1)
NA	1090 (20.3)
Child	
Yes	212 (4)
No	3695 (68.7)
?	300 (5.6)
NA	1168 (21.7)
Partner	
Yes	927 (17.3)
No	3152 (58.6)
?	568 (10.6)
NA	728 (13.5)

Prevalence of risk indicators in relation to periodontitis severity groups

Of the 5375 patients, 4350 were diagnosed with the severe form of adult periodontitis and most subjects were >55 years of age (Appendix S3). The prevalence of females was higher than males. Approximately 2/3 of the mild periodontitis group were non-smoker, whereas in the severe group, this was the case for approximately one-third. Close to one-third of the parents of a patient were reported also to have periodontitis. Overall, numerically the highest predictive value for all variables was observed in the severe periodontitis group.

Prevalence of risk indicators in relation to periodontitis extent groups

Almost half of the patients had generalized periodontitis (n = 2504) (Appendix S4). The gender distribution was much the same over the four extent groups. More than half of the patients in the generalized periodontitis group were >55 years. Approximately 1/3 of generalized group were smokers. Half of the group of patients with incidental periodontitis consisted of non-smokers. More than 1/3 of probands having semi-generalized or generalized adult periodontitis group reported to have parents with periodontitis.

Groupwise comparisons of predictive values of risk indicators and demographic characteristics categorized by diagnostic aspect

Severity

The age of the patient in the sample population as assessed with three defined age groups was not significantly related to disease severity (P = 0.1051) (Table 2). Mainly a child or brother with periodontal problems showed the higher estimates for larger severity of periodontitis, which were significant (P = 0.0009 and P < 0.001, respectively). Also male gender, smoking status, at least one parent or sibling with periodontal problems or a partner with periodontal problems were significantly related to the more severe form of adult periodontitis.

Further subanalysis (data not shown) between smokers, non-smokers and former smokers showed that there were significant differences among all groups: between two severity categories for non-smokers versus smokers (P < 0.0001), non-smokers versus former smokers (P = 0.0004) and smokers versus former smokers (P = 0.0288). There were also significant differences between less severe and more severe periodontitis observed between two severity categories regarding the mean number of years former smokers stopped smoking (less severe: 13.8 (SD 11.1) versus more severe: 9.9 (SD 10.1, P < 0.001)), respectively, and also the number of years that smokers having been smoking differed between the two severity categories (less severe: 23.1 years (SD 10.4) versus more severe: 25.4 years (SD 11.1, P = 0.0017)).

Table 2. **Distribution (predictive value percentage) of demographic characteristics and risk indicators between two severity groups of periodontitis**

Risk indicators	Predictive value percentage: Less severe periodontitis (n = 1025)	Predictive value percentage: More severe periodontitis (n = 4350)	*P*-value for relation
Age			
≥35–≤45	21.2	78.8	0.1051
>45–≤55	17.4	82.6	
>55	19.3	80.7	
Female	21.3	78.7	<0.001*
Male	16.3	83.7	

*Significant.

Extent

The age of the patient in the sample population as assessed with three defined age groups was significantly related to the extent of the disease severity (P = 0.0006) (Table 3). Table 3 shows that family history of periodontitis was significantly related with the severe (semi-generalized and generalized combined) form of periodontitis with estimates varying from 0.39 to 0.56. Also male gender, smoking status and age distribution were significantly related with the larger extent.

Further subanalysis (data not shown) between smokers, non-smokers and former smokers showed that there were significant differences among all groups: between two extent categories for non-smokers versus smokers (P < 0.0001), non-smokers versus former smokers (P = 0.0004) and smokers versus former smokers (P < 0.001). There were significant differences observed between smaller and larger extent regarding the mean number of years former smokers stopped smoking: 12.6 (SD 10.9) versus 9.55 (SD 10.0, P < 0.001), respectively. The number of cigarettes that smokers smoked per day differed also between groups: smaller extent: 11.8 (SD 7.2) versus larger: 14.0 (SD 7.6, P < 0.001).

Using a stepwise multiple regression analysis, the variable selection was made to find the subset of risk indicators that predict higher severity and extent the most (Table 4). Being smoker, having a brother with periodontal problems or being male gender predicted the more severe form of periodontitis. Larger extent as compared to smaller extent of periodontitis was predicted by smoking status, male gender or having a parent with periodontal problems.

Table 3. **Distribution (predictive value percentage) of demographic characteristics and risk indicators between two extent groups of periodontitis**

Risk indicators	Predictive value percentage: Smaller extent periodontitis (n = 1830)	Predictive value percentage: Higher extent periodontitis (n = 3551)	*P*-value for relation
Age			
≥35–≤45	39.7	60.3	0.0006*
>45–≤55	34.8	65.2	
>55	32.0	68.0	
Female	38.2	61.8	<0.001*
Male	28.9	71.1	

*Significant.

Discussion

The current study focused on a periodontal referral population and examined the prevalence of well-recognized risk indicators in relation to extent and severity of adult periodontitis. Being a current smoker was reported by 34.4% of patients. Partner and mother were the most frequently reported family members having periodontal problems, 17.3% and 17.2%, respectively. Most patients were diagnosed with the more severe form (n = 4350) and the generalized extent form (n = 2504) of adult periodontitis. The differences in distribution of risk indicators and demographic characteristics between periodontitis severity and extent categories were calculated. The predictive values of these in relation to periodontitis were analysed statistically and are discussed below.

Smoking

In total, 34.4% of the studied sample reported to be smokers. The observations also showed a significantly higher predictive value for smokers to belong to a periodontitis group with more periodontal destruction. In elderly twin pairs, it is showed that twins with a long lifetime smoking history have a higher level of alveolar bone loss than their twin partners with a low lifetime exposure (13). The association between smoking and the periodontal disease severity in referred periodontitis patients was also investigated in familiar studies (14, 15). Results of their studies have shown that the prevalence of smoking increased with severity and that smokers had higher mean probing depths, more deep pockets, lower percentage of shallow pockets and significantly less mean percentage of radiographic bone support than non-smokers. Similar results are reported on referred chronic periodontitis to a periodontal clinic: proportion of pockets with 4 mm was 33% for smokers and 21% for non-smokers (16). Besides, one has to bear in mind that smoking may interact

Table 4. **Subset of variables (determined by a stepwise multiple regression analysis) that predict severity (mild/moderate versus severe) and extent (incidental/localized versus semi-generalized/generalized) of adult periodontitis at best**

Risk factor	*P*-value
Prediction of severity	
Smoking	0.0529
Brother with periodontal problems	0.0316
Gender	0.0057
Prediction of extent	
Smoking	<0.0001
Father with periodontal problems	0.0194
Mother with periodontal problems	0.0062
Gender	<0.0001

with other factors, including genetics (17), which potentiates periodontal breakdown (18, 19).

In the present study, smoking status was assessed via self-report of which the validity is often questioned because of the widespread belief that smokers are tended to underestimate the number of cigarettes they smoke or to deny smoking (20). According to the World Health Organisation (WHO) World Health Statistics 2015, the prevalence of smoking in the Netherlands has decreased: from 33% (2000) to 24% (2015). It is interesting to observe that the same trend (although with some fluctuation) is apparent in the referral population that was investigated in the current study. Van der Weijden *et al.* (21). reported the prevalence of smokers in the same referral practice to be 43% at the time of 1995–1996, whereas in the current study, a marked overall lower percentage was observed (34%). The decrease in smoking prevalence over the period when data for current publication were collected is illustrated in the Appendix S6.

Gender

The study sample consisted of a higher proportion of females than males. Epidemiological surveys have consistently shown that periodontitis is more prevalent in males than in females (8). Considering the high prevalence (81%) of severe periodontitis in the investigated sample, a higher percentage of males would have been expected. In the previous publication (10), we discussed that the observed gender distribution, which is skewed towards females possibly, can be attributed to the referral bias due to a higher dental awareness and greater willingness by women to seek for the treatment.

Familial aggregation

The participants were questioned by the examining periodontist whether family members had periodontal problems. Approximately half of the sample population did not know whether their family members had periodontitis, which might have introduced information estimation bias. The data revealed that patients were mostly aware about their partners' periodontal condition. There is limited literature available about family studies of probands with adult periodontitis. The influence of genetic and environmental factors was investigated in a large Hawaiian population among nuclear families (age range: 14–60 years) (22). Significant heritability was not detected and common family environment was a major determinant in the variation of periodontal health. Familiar aggregation and computed standard familial correlations were determined (23). The results showed a statistically significant family effect for mean plaque index, but not mean attachment loss. Considering parents, the current study showed a numerically higher percentage of patients reporting their mother rather than a father with periodontitis.

Petit *et al.* (24). studied familial aspects of adult periodontitis in a Dutch population. 24 families were selected at the Academic Center for Dentistry. The results showed that 21% of children from the group of 5–15 years had at least one pocket ≥5 mm with attachment loss. Recently, it was reported that compared to children of two parents with periodontal health, children who have at least one parent with aggressive periodontitis had worse clinical periodontal conditions (25). In particular, the effect of sibling relationship on the periodontal condition was investigated in an epidemiologic study of a group of young Indonesians deprived of regular dental care. The population included 23 family units consisting of three or more siblings. A significant sibling relationship effect for plaque, calculus and loss of attachment but not for pocket depth was observed (26).

In the present study, the prevalence of probands' partner with periodontitis was the highest (17.3%) compared with other family members. The highest predictive value to have severe periodontitis compared to mild or moderate form was estimated for patients who had a child or brother with periodontal problems. Having a father or brother with periodontitis predicted larger extent of the periodontal involvement. The results of the analysis regarding family members was performed only on those subjects who were aware of the condition and provided answer 'yes' or 'no' in the questionnaire. It is difficult to compare results of the current study with available literature about familial aggregation of periodontitis and its association with disease extent or severity. As to our knowledge, a study like the present one which includes information on familial aggregation in a large group of professionally diagnosed adult periodontitis patients has not yet been performed. As stated earlier, a high proportion of the investigated population had a limited awareness regarding periodontal problems of their family members. The impact of this on the estimate of familial aggregation can be interpreted based on previous results (27). They assessed the periodontal status of relatives of aggressive periodontitis patients and evaluated the reliability of the family history report as provided by the proband. If the report provided by the proband was positive, the likelihood of finding periodontitis in that relative was 85.7%, whereas if the report was negative, the likelihood of the absence of periodontitis was 70.6%. Authors suggested that the screening of relatives with a positive family history could be justified as a standard procedure.

The data in this study (Table 4) show that for extent and severity in adult periodontitis, both smoking status and gender emerged as sources of variation. With respect to the family history of periodontitis, a difference between extent and severity was observed with a proband's parents related to extent and a brother with periodontitis related to severity. This observation is consistent with Shearer *et al.* (28). who showed that the children of parents with poor periodontal oral health are themselves more likely to have poor periodontal health. Further research is needed to establish to what extent shared genetic and environmental factors contribute the individual's periodontal status, and may help to predict patient prognosis and preventive treatment need.

The classification approach for cases with periodontitis of Van der Velden (11, 12) uses a combination of the key clinical parameters and age-specific criteria. This approach is not widely used which prevents the comparisons with other

studies. The objective of the classification was to provide a simple means to differentiate between various forms of the disease. This classification method can be utilized for purposes such as estimates of treatment needs, identification of risk factors and disease activity. Analysing a population of never-treated adults, Baelum and López (29) concluded that the proposed classification system is well suited for providing a clear image of the case. The present study is the first to report on the differentiation of extent and severity among an adult periodontitis population in relation to the prevalence of putative risk factors.

Limitations

Several limitations concerning this study were identified. Details are presented in the Appendix S5. A point of concern is that behavioral risk factors are likely to be shared among family members, especially if they live within the same household. Future research should attempt to untangle that web.

Conclusion

Familial aggregation, smoking status, age and gender are factors within the investigated population that were related to extent and severity of adult periodontitis. The practical implication is that addressing smoking cessation and awareness about familial aggregation of periodontal disease should be part of professional dental care.

Clinical relevance

Scientific rationale for the study

The present study is the first to report on the differentiation of extent and severity among an adult periodontitis population in relation to the prevalence of putative risk factors.

Principle findings

Among the referred periodontal patients, the prevalence of smoking was 34.4%, and 37% of the patients had at least one parent or sibling with periodontitis.

Practical implications

Addressing smoking cessation and awareness about familial aggregation of periodontal disease should be part of professional dental care.

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Supporting information

Additional supporting information may be found in the online version of this article.

Appendix S1. The RECORD statement – checklist of items, extended from the STROBE statement.

Appendix S2. Periodontitis classification according to Van der Velden, U.

Appendix S3. Prevalence of demographic characteristics, risk indicators and their distribution among the three periodontitis severity groups.

Appendix S4. Prevalence of demographic characteristics, risk indicators and their distribution among the four periodontitis extent groups.

Appendix S5. Limitations.

Appendix S6. Trend for smoking prevalence over the observation years.

Chapter 5
Online appendices

General discussion, summary and conclusions

Periodontal disease is an inclusive term that encompasses various oral inflammatory pathologies, of which the most prevalent are gingivitis and periodontitis. Gingivitis is an inflammation of the gingiva that is largely reversible. It is a precursor to and prerequisite for periodontitis (Könönen et al., 2019; Lang et al., 2009). Periodontitis destroys the attachment apparatus of the tooth, including the alveolar bone, ultimately resulting in tooth loss. Periodontitis is inflammatory in nature and – alongside dental caries – the most common disease of humans, affecting 50% of adults in a milder form; notably, the rate increases to more than 60% in those aged >65 years (Genco & Sanz, 2020). The loss of teeth leads to issues such as inadequate nutrition, low self-esteem, lack of confidence, and poor quality of life (Hassan et al., 2022). Patients with periodontitis typically tend to exhibit one or more risk factors, although similar risk factors can be identically exhibited in patients with largely varying degrees of disease severity. By contrast, some younger patients with severe disease, such as those with localized, rapidly progressive periodontitis, may not exhibit any of the typical risk factors (Slots, 2017). This thesis aimed to gather information about the risk factors associated with periodontitis. Among them, diabetes **(Chapters 1–4)**, smoking **(Chapter 5)**, and familial aggregation **(Chapter 5)** were the main topics. In the following paragraphs, the chapters of the thesis are discussed in the light of existing literature.

In recent decades, the interrelationship between periodontitis and diabetes has been extensively discussed by not only academics but also association representatives and even clinicians. In the early 1990s, periodontitis was referred to as the "sixth complication of diabetes" (Löe, 1993). Furthermore, in 2003, the American Diabetes Association acknowledged that periodontal disease is often found in people with diabetes (Lowe, 2001; Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003;). Since then, researchers have attempted to confirm the potential two-way relationship and synergy between periodontitis and diabetes; however, the evidence remains contradictory from both clinical and epidemiological perspectives.
A practice-based retrospective study in Germany used the Finnish Diabetes Risk Score questionnaire (Lindström et al., 2003 Schmalz et al., 2021) as a diabetes screening method in patients diagnosed with Stage III or IV periodontitis (Caton et al., 2018; Papapanou et al., 2018; Tonetti et al., 2018). Individuals with positive scores were referred for further examination. The study found diabetes mellitus (DM) to be prevalent among 11.2% of patients with severe periodontitis. By contrast, German national data for the 50–59 age group – the same age group included in the aforementioned study – revealed a prevalence almost twice as low at 5.7%. The authors suggested that this discrepancy may be explained by the interrelationship between periodontitis and diabetes. Moreover, a study conducted in London over the course of 12 months aimed to investigate the prevalence of potentially undiagnosed type 2 diabetes mellitus (T2DM) in patients with chronic

periodontitis attending a predominantly National Health Service general dental practice (Goh et al., 2021). The results indicated that the prevalence of previously undiagnosed T2DM was 5% and that of prediabetes was 23%. A statistical analysis revealed that the test results from neither the Finnish Diabetes Risk Score nor the final glycated hemoglobin (HbA1c) test were significantly correlated with the degree of periodontitis.
A practice-based study conducted in the Netherlands collected data from a convenience sample of 1,276 randomly selected dental records; 588 belonged to patients attending a general dental clinic and 688 to patients attending two clinics restricted to periodontology (Nesse et al., 2010). The information regarding diabetes was self-reported by the participants through another type of questionnaire. The prevalence of diabetes among the group of control patients from a general dental clinic was 1.6%, whereas that among patients with periodontitis from the general clinic and the two periodontal clinics was 5.5% and 5.1%, respectively. A study conducted at the Academic Centre for Dentistry Amsterdam in the Netherlands [ACTA] showed that the number of individuals with self-reported diabetes mellitus was not significantly different between the controls (2.8%) and patients with periodontitis (4.0% for mild/ moderate periodontitis, and 7.7% for severe periodontitis) (Teeuw et al., 2017). The prevalence of diabetes among periodontitis patients from both Dutch studies is close to the estimated national prevalence of diabetes in the Netherlands, which currently is in the range of 6.25%.

The national prevalence is however higher than that found among a large group of patients with periodontitis in the study in **Chapter 1** (3.7%). This percentage was retrieved from a self-reported analysis of 5,375 patient records of a clinic restricted to periodontology. This clinic is situated in Utrecht, which is the region with the highest prevalence of diabetes in the Netherlands (4.6-5.1%) (Diabetes mellitus bij ouderen, Krulder, 2010). It therefore does not support the presumed interrelationship between periodontitis and diabetes. Also, the prevalence of diabetes from the clinic was from predominantly "controlled" diabetic population and further analysis showed not relationship with the extent and/or severity of periodontitis. The strength of this study is that it includes one of the largest study groups of true periodontal patients assessed for diabetes prevalence to date, based on a full mouth periodontal examination. However, a potential bias could exist in the study since it failed to account for regional differences in the Netherlands due to being limited to one center. Therefore, a multicenter design across different provinces in the Netherlands, and preferably other countries, is required for the findings to be generalizable. In support of the findings in **Chapter 1** is a study that used data extracted from 60,174 patient records from the largest dental school in the Netherlands (ACTA). It found that self-reported DM among patients with periodontitis was 6%, which is also within the range of the estimated national prevalence of DM in the Netherlands (Beukers et al., 2017). However other work from ACTA showed that the prevalence of pre-diabetes (HbA1C = 5.7–6.4%)

among subjects with severe periodontitis was higher compared to subjects with mild/moderate periodontitis and controls, respectively (p=0.024) (Teeuw et al., 2017).
In light of the findings presented in **Chapter 1**, it was decided that it would be interesting to conduct a review to summarize relevant literature on our question regarding the prevalence of diabetes among periodontal patients. The authors employed explicit methods to search, critically appraise, and synthesize the world literature systematically, which allowed to consider the whole range of relevant findings from research on the current topic. This helped to determine whether the scientific findings are reliable and generalizable across populations or vary significantly by particular subgroups.

The findings presented in **Chapter 2** do not fully support the findings of **Chapter 1.** **Chapter 1** reflects a lower percentage of patients with periodontitis and diabetes (3.7%) in perspective to the general public irrespective of their periodontal status (4.5-6.1%). While **Chapter 2** showed that the worldwide prevalence and odds of having DM are higher in periodontitis populations than specifically in people without periodontitis. The prevalence of DM was 13.1% and 9.6% among subjects with and without periodontitis, respectively. The latter result indicates that the data derived from the included studies were slightly skewed toward metabolic disease conditions, as the global diabetes prevalence is reported to be 8,5-9.8% for adults (International Diabetes Federation [IDF] Atlas, 2021; Noncommunicable diseases Risk Factor Collaboration, 2016; WHO, 2016). Further, in the results of **Chapter 2**, 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. Taking into consideration that 68% of adults with diabetes live in the 10 countries with the highest number of people with diabetes (mostly allocated in Asian region), it helps to explain the skewed results (IDF Atlas, 2021).
The data in **Chapter 2** also suggest a bias toward a relatively elevated prevalence of diabetes among participants with periodontitis. Diabetes prevalence in people with periodontitis was 6.2% when self-reported, whereas it was 17.3% when clinically assessed. This in turn suggests that, relative to clinical assessments, the prevalence of diabetes is underestimated when it is self-reported. To prevent any potential prejudice, this factor should be considered in future dental research. Additionally, the prevalence of clinically diagnosed diabetes was almost twice as high as the WHO's global estimate from 2015. This again suggests that the data may be skewed in favor of diabetes.
A more recent systematic study also assessed the epidemiological relationship between periodontitis and T2DM (Wu et al., 2020). In a subgroup analysis, the authors assessed T2DM prevalence among periodontitis versus non-periodontitis patients. Three studies with a total of 1,956 participants were eligible for the meta-analysis (MA). The included studies did not reveal any significant heterogeneity.

Moreover, the results revealed that compared with participants with no periodontitis, those with periodontitis had significantly higher odds of having T2DM (odds ratio [OR] 4.04, 95% confidence interval [CI] [2.48–6.59], p < 0.001). Furthermore, a systematic review (SR) and MA studied the presumed bidirectional association between periodontal disease and DM (Stöhr et al., 2021). When comparing individuals with periodontitis with those without, the summary relative risk (sRR) for incident DM was 1.26 (95% CI [1.12, 1.41]). This is consistent with the findings presented in **Chapter 2**, which reveal the OR for patients with DM to be 2.27 among individuals with periodontitis compared with those without (95% CI [1.90; 2.72], p < 0.00001). When these two statistical outcomes are compared, the OR of 2.27 reflects a larger effect of the periodontitis–DM relationship than the sRR of 1.26 (Ranganathan et al., 2015). The explanation for this is that when an association exists between an exposure and an outcome, the OR exaggerates the estimate of their relationship. Thus, when the risk ratio (RR) is more than 1.0, the OR is higher than the RR (Ranganathan et al., 2015). Furthermore, a position paper by the International Diabetes Federation–European Federation of Periodontology (IDF–EFP) workshop on periodontitis and DM concluded that individuals with periodontitis have a significantly higher risk of developing T2DM, which is represented by a hazard ratio range of 1.19–1.33 (Sanz et al., 2018).

The findings of an expert panel at the 2013 joint American Academy of Periodontology (AAP) and EFP workshop on "Periodontitis and Systemic Diseases" concluded that "reported associations do not imply causality and the establishment of causality would require new studies that fulfill the Bradford Hill or equivalent criteria" (Chapple et al., 2013). A few years later, DM was recognized as one of only two true risk factors for periodontal disease (along with smoking) and incorporated as part of the "grading" component of the new classification of periodontal diseases by the AAP and the EFP (Caton et al., 2018; Papapanou et al., 2018; Tonetti et al., 2018). Furthermore, studies have recurrently indicated that observational studies identifying any association between periodontal diseases and systemic conditions should strictly adhere to a more stringent pathway to publication (Mark Bartold & Mariotti, 2017). To this end, employing the Bradford Hill criteria and the STROBE (STrengthening the Reporting of OBservational Studies in Epidemiology) statement has been recommended for the studies that report any periodontal systemic observational study (Hill, 1965; Vandenbroucke et al., 2007). In epidemiological research, an existing association between an environmental factor and a disease can be evaluated for causality based on the Bradford Hill criteria. In other words, an evaluation of the strength of association can be conducted based on explainable mechanisms within the context of epidemiology. The list of criteria includes the strength of association, consistency, coherence, specificity, temporality, dose–response relationship, biological plausibility, (quasi) experimental evidence, and analogy. Initially, these criteria were mainly used to interpret the relationship between lung cancer and smoking.

The Bradford Hill criteria however are not yet widely applied within oral health care. Studies are continually appearing where the biological pathway is unclear but credit is given for a significant association or correlation without a proper translation to a clinical effect size and consequently clinical relevance interpretation. This is especially common in the area of systemic diseases and oral disorders. A recent position paper from the Canadian Dental Hygienists Association reviewed the most recent evidence on the relationship between T2DM and periodontitis to interpret observations of a causal relationship (Lavigne & Forrest, 2021). SRs with or without an MA of randomized controlled trials (RCTs) or umbrella reviews of SRs and MAs of RCTs published in English between 2007 and 2019 were included. The evidence for causality was determined using the Bradford Hill criteria based on a summary of the evidence (Hill, 1965). The authors' analysis failed to support the supposition that a causal relationship exists between periodontitis and T2DM.

To acknowledge the treatment of periodontitis and its relationship to glycemic control in people with DM, a review evaluated periodontal treatment versus no intervention or usual care by Cochrane SR (Simpson et al., 2022). This publication is a part of the review that initially was published in 2010 and first time was updated in 2015. An absolute reduction in HbA1c of 0.43% 3–4 months after treatment for periodontitis showed a moderate certainty evidence (30 studies; 2,443 analyzed participants). Similarly, after 6 months, an absolute reduction in HbA1c of 0.30% was found (12 studies, 1,457 participants), and after a period of 12 months, an absolute reduction of 0.50% was found (one study, 264 participants). The authors concluded that moderate-certainty evidence exists that periodontal treatment using subgingival instrumentation provides a clinically significant improvement in glycemic control in people with both periodontitis and DM compared with no treatment or usual care. Authors imply that future studies assessing the effect of periodontal treatment compared to no treatment/usual care doubtfully would change the conclusion of their literature review (Simpson et al., 2022). To examine this more deeply, the aforementioned review included some studies that did not report baseline HbA1c values, while others had a wide range of HbA1c, representing the whole scope of the literature assessing the effect of periodontal treatment on glycemic control. Thus, in the case of a patient having poor glycemic control (i.e., >8.5% HbA1c), even a reduction of 0.5% would not make him/her a nondiabetic one. A comprehensive SR evaluated nonexperimental, epidemiological evidence for the effects of periodontal disease on diabetes control, complications, and incidence (Borgnakke et al., 2013). The authors identified that a paucity of evidence highlights the effects of periodontal disease on glycemic control.
A reduction in HbA1c is a well-validated and acknowledged surrogate for glycemic control and long-term microvascular complications. It is used by medical doctors in daily clinical practice for counseling patients and has become the standard outcome measure in different experimental methods for a variety of DM therapies (European Medicines Agency [EMA], 2012; U.S. Department of Health and Human

Services Food and Drug Administration, 2008). In this respect, other interventions may provide a greater impact than periodontal treatment, such as weight loss. In one study, a linear relationship between weight loss and HbA1c reduction was observed from model-based analyses (Gummesson et al., 2017). For each 1 kg of reduced body weight the reduction of HbA1c 0.1 percentage points was estimated for the overall population. Additionally, weight loss–dependent reductions in antidiabetic medication were also demonstrated based on the collected trial data. In view of these results, losing 5 kg is equivalent to the effect of periodontal treatment if the best-case scenario is taken (0.5% reduction) compared with the results of the SR on the effect of periodontal treatment on HbA1c levels (Simpson et al., 2022).
The prevalence of overweight (body mass index, BMI, between 25 and 30kg/m2) or obesity (BMI of 30kg/m2 or higher) is highly prevalent (around 85%) among people with diabetes, which can complicate the condition in different ways (Hjartåker et al., 2008; Nianogo et al., 2022; Whitmore, 2010). If an obese person who weighs 110 kg could lose 20 kg, for example, this would result in a double effect on HbA1c levels compared with periodontal treatment itself. Furthermore, recent research identified the association between physical exercise and HbA1c levels in 2,559 Korean patients diagnosed with diabetes (Yun et al., 2022). In male patients with diabetes, physical exercise, including walking and resistance exercises, was associated with controlled HbA1c levels <6.5% with an OR of 1.85 (95% CI [1.17–2.92], $p < 0.05$). Considering the aforementioned discussion, weight loss or physical exercise and its effect on presumably long-lasting glycemic control, compared with the prevailing SRs reporting HbA1c improvements up to 12 months, should have a greater impact on the well-being of a patient with diabetes compared with the periodontal treatment itself (Baeza et al., 2020; Cao et al., 2019; Simpson et al., 2022). Even an extreme form of periodontal treatment, such as a full mouth extraction of hopeless teeth in people with T2DM, would result in average HbA1c reductions of 1.23% at 3 months and 1.37% at 6 months after treatment (Khader et al., 2010). The authors concluded that full-mouth tooth extraction resulted in an improvement in glycemic control among diabetic patients. The size of the reduction was clearly greater than that reported by earlier studies investigating nonsurgical periodontal treatment. However, these patients would still be considered to have diabetes. At baseline, the mean HbA1c level was 8.6% in the treatment group, which decreased significantly from 8.6% at baseline to 7.3% after 6 months.

To broaden the observations regarding the possible effect of diabetes on the whole dentition, in light of the previous findings of an association between diabetes and more severe periodontitis disease, the study presented in **Chapter 3** systematically assessed the risk of tooth loss in patients with DM. It found that moderate-certainty evidence exists for a small but significantly higher risk of tooth loss in patients with DM compared with those without DM.

A descriptive analysis demonstrated that six of the included studies indicated a significantly higher risk of tooth loss in DM. This was confirmed by the MA, which revealed an RR of 1.63 (95% CI [1.33; 2.00], $p < 0.00001$). The risk of tooth loss in patients with DM was also higher when only patients with T2DM or studies with a cross-sectional design were considered. Patients with poor diabetic control presented a significantly increased risk of tooth loss. Due to this increased risk, patients with diabetes should receive special attention from dental care practitioners regarding oral disease prevention. To address the same theme, a subsequent systematic review and meta-analysis of observational studies was published. It was designed to examine the association between T2DM and tooth loss (Ahmadinia et al., 2022). The authors have concluded that T2DM is associated with increased risk of tooth loss. MA of unadjusted and adjusted results showed that T2DM significantly increased the risk of tooth loss, and unadjusted OR was 1.87 (95% CI [1.62-2.13], $p < 0.001$), while the adjusted OR was 1.20 (95% CI [1.10-1.30], $p < 0.001$), respectively.

In a study involving 144 patients (70 with and 74 without DM), the authors reported no statistically significant difference in the mean caries prevalence between the two groups (Arrieta-Blanco et al., 2003). The prevalence of carious lesions was 7.39% in patients with DM and 6.91% in those without. Another study demonstrated that the prevalence of dental caries was markedly higher in people without diabetes (32.3%) than in patients with diabetes (13.6%; $p < 0.001$) (Bharateesh et al., 2012). The authors suggested that individuals with diabetes may experience fewer dental cavities since their diets often contain more protein and fewer fermentable carbohydrates. In a related study, the authors found no differences in the number of caries lesions between patients with type 1 DM (T1DM) and a group of healthy subjects (Miralles Jorda et al., 2002). Almost 35 years ago, a study determined the prevalence of dental caries, the Decayed, Missing, and Filled Teeth (DMFT) index score, and treatment needs in a group of patients with DM and compared them with a control group (Bacić et al., 1989). The results revealed no difference in the prevalence of caries or mean number of teeth with fillings between the groups. However, a sub-analysis revealed that patients with T1DM did have a significantly higher number of teeth with fillings (4.05 vs. 2.22) than patients with T2DM ($p < 0.001$). No difference existed in the caries experience in connection with duration of DM, diabetic control, or diabetic complications. Regarding tooth loss, the number of extracted teeth per subject was significantly higher in the group with DM (12.3) than in the control group (9.7) ($p < 0.01$). A sub-analysis demonstrated that a significantly higher number of extracted teeth was in a group of patients with T2DM than those without (14.1 vs. 10.4, respectively; $p < 0.001$) (Bacić et al., 1989). This may have introduced a bias to the data with respect to caries prevalence as presumably decayed teeth were extracted.

A practice-based retrospective study in Germany that included patients with Stage III or IV periodontitis revealed that individuals with newly diagnosed DM had significantly more missing teeth than those without the condition at 9.42

versus 4.99, respectively (p = 0.01) (Schmalz et al., 2021). Furthermore, a cross-sectional study of 15,965 Hispanic/Latino individuals from the United States found a substantial and positive correlation between having at least nine missing teeth and uncontrolled diabetes (defined as diabetes with HbA1c levels ≥7%) with an OR of 1.92 (95% CI [1.44–2.55], p < 0.05; Greenblatt et al., 2016). The finding of people with uncontrolled DM having more missing teeth corresponds to the results presented in **Chapter 3** of the thesis. A SR evaluated the difference in tooth loss between patients with T2DM and DM-free subjects (Wu et al., 2020). The results indicated that patients with T2DM had lost on average 2.22 more teeth than the controls (weighted mean difference = 2.22, 95% [CI 0.94–3.49], p = 0.000). The results were strengthened by no publication bias being detected. However, a shortcoming in the included studies was that they did not consider the reason for tooth loss. Self-reported tooth loss has also been demonstrated to possibly not be accurate. Although clinical examination is the optimal method for determining tooth loss, self-reporting maybe sufficiently accurate for a high number of participants. A study performed an extensive analysis of data from the National Health and Nutrition Examination Survey (NHANES) database, evaluating the differences in trends in tooth loss for adults with and without DM (Luo et al., 2015). Adults with DM were revealed to have lost more teeth than those without DM (p < 0.001). However, over the observation period from 1971 to 2012, the number of missing teeth decreased from 11.2 to 6.6 for those with DM and from 9.4 to 3.4 in those without DM. Nevertheless, the rate of decrease between these groups did not differ (p = 0.36). Another study conducted in Japan determined the number of natural teeth and functional tooth units required to maintain adequate self-assessed chewing function (Ueno et al., 2008). Maintaining 20 or more natural teeth and at least eight functional tooth units were considered crucial for reducing the likelihood of self-assessed chewing difficulties. The results indicated that having an average of 23.4 total natural teeth allowed subjects to eat all 15 tested food items. Relating this conclusion to the NHANES data indicates that, on average, patients with diabetes still have sufficient masticatory function.

Different explanations may be introduced for explaining the relationship between diabetes and tooth loss, such as patients with diabetes having a higher prevalence of xerostomia (12.5–53.5%) than those without diabetes (0–30%) (López-Pintor et al., 2016; Verhulst et al., 2019). Both xerostomia and periodontal disease are risk determinants for the occurrence of tooth loss and edentulism (Guggenheimer & Moore, 2003; Martinez-Canut, 2015). Various other factors may mediate an effect of diabetes on tooth loss. A good example is diabetes being a well-known risk factor for depression, while depression may lead to tooth loss through poor oral health and changes in salivary immunity and oral flora (Chireh et al., 2019). In addition, some scientists have suggested that cognitive impairment is relatively frequent in people with diabetes, and that it is associated with poor oral care and ultimately tooth loss and edentulism (Naorungroj et al., 2013, Wennberg et al., 2017). It also appears from the literature that patients with diabetes have tendency to

visit the dentist less frequently as compared to people without diabetes (Macek et al., 2009). For example, a study conducted in the Netherlands has shown that approximately a quarter of the participants with diabetes did not attend dental appointments regularly (Verhulst et al., 2019a). Studies have shown that the presence of diabetes and lack of a dental visit in the past year were significantly associated with excess tooth loss.
The WHO databank indicates that caries remains prevalent in most countries worldwide, with some reporting 100% incidence in their populations. Severe periodontal disease is estimated to affect 5–24% of the population, and the incidence of complete edentulism has been estimated at between 7% and 69%. In view of the findings presented in **Chapter 3** of the thesis, the subsequent literature investigation covers the question of whether people with diabetes are at a higher risk of edentulism. **Chapter 4** presents an SR of edentulism risk in patients with diabetes. It reveals that weak evidence exists that among individuals diagnosed with diabetes, the prevalence of edentulism is higher than that among those without diabetes. In total, 8.7% of the populations from the included studies were edentulous. The weighted mean prevalence of edentulism among patients with and without diabetes was 14.1% and 7.5%, respectively. The overall OR for patients with diabetes being edentulous compared with people without diabetes was 2.49 (95% CI [1.75; 3.54], $p < 0.00001$). Therefore, patients with diabetes should be cognizant that they are at a slightly higher risk of tooth loss (see also **Chapter 3**), which eventually leads to edentulism.

In a literature review of other systemic conditions, completely edentulous patients were found to be at higher risk of diabetes (OR = 1.82) (Felton et al., 2009). By contrast, in our results presented in **Chapter 4**, the overall OR for patients with diabetes being edentulous compared with those without diabetes was 2.49 (95% CI [1.75; 3.54], $p < 0.00001$). The difference may for instance be clarified by the fact that compared to the data analyzed in 2009 (Felton et al., 2009), **Chapter 4** has included 3 new published studies published after 2009 with approximately 22.000 participants. Jacob et al. (2021) investigated the association between diabetes and edentulism in adults from 40 low- and middle-income countries. Overall, the prevalence of edentulism was 6.0% and the prevalence of diabetes 2.9%. There was a positive and significant association between diabetes and edentulism in the overall sample with an OR of 1.40 (95% CI [1.18; 1.66], $p < 0.001$). A sub-analysis demonstrated significant associations, where the OR for people with diabetes being edentulous in low-income countries was 1.78 (95% CI [1.06; 1.08], $p < 0.001$) and that in middle-income countries was 1.24 (95% CI [1.04; 1.47], $p < 0.05$) (Jacob et al., 2021).
The prevalence of self-reported edentulism and its associated risk factors among communitydwelling adults aged 45 years and older in China was studied (Ren et al., 2016). The data of 17,167 subjects were collected from the National Baseline Survey (2011–12) of the China Health and Retirement Longitudinal Study.

The prevalence of edentulism was 8.64% among Chinese adults aged 45 years and older. After adjusting for a wide range of variables, such as gender, place of residence, and income level, diabetes was found not to be significantly associated with edentulism (Ren et al., 2016). These epidemiological variations in distribution and the prevalence of complete edentulism between developed and lessdeveloped countries may be associated with a complex interrelationship between cultural, individual, access-to-care, and socioeconomic factors (Petersen et al., 2005). Moreover, the parameters how diabetes and edentulism were estimated, vary between studies, which could partly explain the differential results. For example, diabetes has been self-reported or defined using biological parameters (e.g., HbA1c and fasting glucose), while edentulism has been assessed based on self-reports or examinations by dental care professionals. Furthermore, completely edentulous patients were found to be at a higher risk of poor nutrition and having diabetes (OR = 1.82; Felton 2009). Therefore, an interplay might exist between the two, which may cause bias. On the other hand, the full-mouth extraction of teeth with terminally advanced periodontitis leads to a small but significant decrease in HbA1c levels in T2DM. For example, in a study conducted in Jordan, HbA1c levels dropped from 8.6% at baseline to 7.4% 3 months post-extraction and to 7.3% after 6 months (Khader et al., 2010). Despite decreasing after the removal of all teeth, the HbA1c levels were still above the threshold of 7%, and thus, the patients were still considered to have DM.

In the existing literature, the interpretation of self-reported tooth loss might not be highly accurate. Although clinical examination is the optimal method for determining tooth loss, some studies have used self-reporting to determine this outcome. Another notable shortcoming of the discussed studies is that they have not considered the reason for tooth loss. The conversion of research findings into daily clinical practice is a challenge in evidence-based dental practice. The acceptance of successful research outcomes in clinical practice is possible when the most reliable research is designed with an applicable endpoint evaluation (Shah et al., 2017). In periodontal research, a few accepted endpoints are used frequently, as they are believed to be the gold standard for measuring periodontal disease and treatment outcomes. They are mostly indirect (i.e., surrogate) measures as primary outcome variables, such as mean changes in the probing pocket depth or clinical attachment level. Surrogates are used to gather quick interpretations at an economical cost, where various treatment modalities lead one to expect only slight differences and/or the observation period is too short to reach the true end-point. However, one problem with the aforementioned surrogate outcomes is that they must accurately reflect the true end-point of tooth loss and not lead to either false-positive or false-negative conclusions (König et al., 2002). Ideally, research should distinguish all-tooth mortality from periodontal- or caries-tooth mortality, for example. Although the research presented in **Chapters 3** and **4** does not categorize data according to the causes of tooth loss,

it represents the true end-points – namely tooth loss and eventually edentulism – in relation to DM.
Most oral and systemic diseases have multifactorial social, biological, and psychological backgrounds as known predictors and causes. They should be controlled for to obtain proper epidemiological estimates of the relationships of interest. Thus, epidemiological studies investigating solely oral or systemic diseases must consider a myriad of individual- and environment-level variables, as together they form a complex web of common risk factors behind oral and systemic diseases (Raittio & Farmer, 2021). This is one of the main challenges encountered while conducting the SRs presented in **Chapters 2**, **3**, and **4**. It was nearly impossible to account for the variables at the individual- and environment-levels to purify the findings of the assessed literature. As a side note, researchers in the future should adhere more rigorously to guidelines for conducting and reporting SRs/MAs and evaluate underlying primary literature more carefully (Taylor et al., 2021).

Research articles today tend to provide far-fetched theories on relationships in their discussion sections despite major methodological concerns. Notably, that some relationship exists between the risk factor and a disease, indicates an estimated statistically significant outcome. While an indication of statistical significance does not provide information about the strength of the association (effect size), some misinterpret statistical significance to indicate effect magnitude. Findings with lower probability (p) values (e.g., $p < 0.001$) are misinterpreted as having a stronger effect than those with higher p values (e.g., $p < 0.05$). In general, instead of focusing on statistical significance, studies should indicate the clinical significance of their findings (Ranganathan et al., 2015). It is crucial that the relationship between oral and systemic diseases is investigated with a more critical approach and more robust methods than before, particularly if the intent is to advance our understanding beyond descriptive associations. While there is merit in publishing studies that use observational data, when robust techniques are not applied to account for potential biases, authors should be cognizant of the limits to causal inference and of stretching their conclusions accordingly. Furthermore, to refine and scale up the research direction of the periodontal–systemic link, the UK-established PROSpECT (Periodontal Research on Multimorbidity and Systemic Health Clinical Study Group and Research Consortium) encourages collaborative working to create a methodological consensus for study design parameters. It has reached an agreement for several research design scarcities—establishing intervention and control arm criteria, target end points, standardized criteria for treatment success, recruitment strategies, and follow-up duration, all of which are critical steps in designing robust studies (Pavitt, 2020). Epidemiological studies demonstrate in increased risk of a disease by probably one of the most widely employed statistic parameter in risk factor research which is OR. It is considered as the predominant index of effect size (Bland &

Altman, 2000).
Researchers claimed that when certain conditions are met (e.g., population rates of "cases" <10%) and peculiar research designs are used, the OR provides a good approximation of the RR (Hosmer & Lemeshow, 2000). However, scholars have also recognized that the OR does not provide a good approximation of the RR when disease rates do not fall below 10% (Altman et al., 1998; Davies et al., 1998; Sinclair & Bracken, 1994). *"When based on the same data, an OR will always differ from zero more often than the RR"* (Deeks, 1998; Sackett et al., 1996). The issue of the OR in epidemiological studies has been thoroughly discussed, and one study proposed a new method for interpreting it (Chen et al., 2010). The method is based on *"interpreting the size of the OR by relating it to differences in a normal standard deviation calculated through a comparison of the respective probabilities"* (Chen et al., 2010). The calculations indicate that *"OR = 1.68, 3.47, and 6.71 are equivalent to Cohen's d = 0.2 (small), 0.5 (medium), and 0.8 (large), respectively, when the disease rate is 1% in the nonexposed group; Cohen's d <0.2 when the OR <1.5; and Cohen's d >0.8 when the OR >5"*. It would be useful to have values with corresponding qualitative descriptors that estimate the strength of such associations; however, no consensus has been reached to date as to what those OR values might be. Our main research results presented in ORs, namely those regarding DM prevalence among periodontal patients (in **Chapter 2**) and edentulism among diabetic patients (**Chapter 4**) were 2.27 and 2.49, respectively. These "translate" into a moderate association between the aforementioned investigated conditions, which were statistically significant for both cases. In **Chapter 3**, the RR of tooth loss among diabetic patients is reported to be 1.63. This is a good approximation of the OR, which would be considered to also have a moderate association with a statistical significance.

Periodontitis is an infection-driven inflammatory disease in tooth supporting tissues in which the primary etiological factor is the subgingival biofilm. One phenotype of this disease that has been identified specifically in young circumpubertal individuals demonstrates a rapid rate of progression that result in precocious loss of teeth (Albandar, 2014). Studies have reported that this phenotype, known as aggressive periodontitis (and currently most likely classified as Stage III or IV grade C periodontitis), presents familial aggregation (Caton et al., 2018; Papapanou et al., 2018; Tonetti et al., 2018). The aggregation of cases in the same family is estimated to be 50%, and both vertically transmitted genetic factors (i.e., those responsible for microbial colonization or host response) and shared environmental factors (e.g., individual oral hygiene and smoking) can increase the chances of periodontitis development (Haubek, 2010; Könönen & Müller, 2000; Meng et al., 2011; Michalowicz et al., 2000). Although specific genes responsible for periodontal disease remain to be identified, a series of conducted research that used using different experimental designs have addressed that genetic factors strongly contribute to periodontitis susceptibility.

A study in the United States evaluated a group of largely African American families in which an older sibling had been diagnosed with localized early-onset periodontitis (Boughman et al., 1992). The results indicated a 50% chance of a younger sibling also developing localized early-onset periodontitis. This type of periodontitis develops as the individual passes through puberty, which is a defined and limited time period, as opposed to gradually developed periodontitis, which can begin and then progress across the entire adult life span; therefore, the results of susceptibility studies of localized early-onset periodontitis may not be transferable to chronic adult periodontitis (Boughman et al., 1992). In addition, the results of studies conducted in the Netherlands and Indonesia have suggested that periodontitis has a genetic basis for the susceptibility of the disease. A statistically significant clustering of periodontitis cases has been found within families (Van der Velden et al., 1989; Van der Velden et al., 1993). However, using a familial study design to distinguish between the relative contribution of genetics versus environmental conditions to disease susceptibility continues to be challenging. A compelling experimental research method for dissecting genetic from environmental factors is the twin study model. Michalowicz et al. (2000) reported the results of a cross-sectional study of adult twins, among whom 64 were monozygotic and 53 were dizygotic. Approximately 50% of the variance observed in periodontitis susceptibility was considered to be due to genetic factors after controlling for smoking, oral hygiene, and the use of dental services.

A paper reporting summary measures of heritability in human studies concluded that a considerable proportion of the variation of periodontitis in humans is attributable to heritable factors (Nibali et al., 2019). This measure of heritability ranged from 0.07 in genome-wide association studies to 0.29 in twin and family studies combined. It is critical to emphasize that next to genetic variances, shared environmental factors (e.g., oral hygiene and smoking) can increase the risk of developing periodontitis (Haubek, 2010; Könönen & Müller, 2000; Meng et al., 2011). Thus, elucidating these elements of susceptibility and the familial component of this disease is critical for understanding the disease pathogenesis.

The available literature regarding the impact of different family and parent characteristics on periodontal diseases in children and adolescents was systematically reviewed (Tadakamadla et al., 2020). The data indicated that mainly three socioeconomic status factors, namely income, education, and occupation, are significantly associated with periodontal diseases in children. Although the association between parents' smoking practices, level of periodontal diseases, and children's periodontal status was found to have been explored in only a few studies, the findings have indicated that children who are exposed to passive smoking and who have parents with periodontal diseases are at greater risk of periodontal diseases themselves (Tadakamadla et al., 2020).

In a study of 20 married couples, the spouses of patients with periodontitis were found to have worse periodontal disease than those of patients without periodontitis (Von Troil-Linden et al., 1995). Gingival suppuration, calculus, and deeper periodontal pockets tended to occur more frequently in spouses married to patients with periodontitis than in those married to patients without periodontitis. Therefore, it not only seems that suspected periodontal pathogens are transmitted between family members but also that this transmission resulted in the initiation of periodontitis in the recipient's spouse. The findings in **Chapter 5** reveal a numerically higher percentage of adult periodontitis patients reporting their mother rather than their father having periodontitis. This could be attributed to a higher dental awareness and greater willingness of women to seek treatment (Lipsky et al., 2021). Monteiro et al. (2021) investigated the impact of parental periodontal disease on the acquisition of oral pathogens in offspring in a longitudinal interventional case-control study. This highlights the critical role played by parental disease in microbial colonization patterns in offspring and the early acquisition of periodontitis-related species. In another study, the distribution and possibility of the transmission of *Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans* were assessed in four families (Petit et al., 1993). The results indicated that the two putative periodontal pathogens were transmitted between parents and their children. The results in **Chapter 5** indicate that the chance of having severe periodontitis was higher if the patient from the studied periodontal population had a brother with periodontitis. In total, 37% of the participants had at least one parent or sibling with periodontitis. This underscores the need for greater surveillance and preventive measures in the families of periodontitis patients. For instance, relevant standard questions could be added to social and dental anamneses.

Tobacco smoking is one of the risk factors for periodontal disease, as it increases periodontal bone loss and compromises periodontal healing (Van der Weijden et al., 2001). Studies have found that after 10 years of supportive periodontal treatment, smokers exhibit deeper periodontal pockets and higher bleeding on probing scores than nonsmokers (De Wet et al., 2017), and that smoking impairs the effect of nonsurgical periodontal treatment (Van der Weijden et al., 2019). Of the periodontitis population (N = 5,375) in the cross-sectional study presented in **Chapter 5**, 34% were smokers. Smoking affects the course of periodontitis through impairing immunological and vascular mechanisms. During the last 30 years, a steady decline in the prevalence of smoking has been observed (Dai et al., 2022). In some regions, such as Australia, the USA, and Central Latin America, a decrease in smoking >30% has been observed. Despite this reduction, there were still 1.1 billion smokers throughout the world in 2019. Smoking supposedly caused 7.7 million deaths globally in 2019 (Theilmann et al., 2022), with one in five deaths being in males (Centers for Disease Control and Prevention, 2010). Nevertheless, an increase in smoking

prevalence of 10–20% has also been observed among Eastern European females (Reitsma et al., 2021).

The results in **Chapter 5** also demonstrate that smoking status is related to the extent and severity of adult periodontitis. For both total periodontitis and severe periodontitis situations, population-based data from the United States and Norway reveal comparable results (Eke et al., 2015; Holde et al., 2017). The prevalence of periodontitis in the United States was 38.3% for nonsmokers and 66.6% for smokers. A Norwegian study reported a prevalence of 45.4% for nonsmokers and 70% for smokers. Specifically, the severe form of periodontitis was more prevalent among smokers than nonsmokers at 18.9% and 5.5%, respectively. In the United States, the rate was 18.4% and 7.4%, respectively (Basavaraj & Khuller, 2011; Beklen et al., 2022).

An SR investigated the association between smoking and periodontitis incidence or progression (Leite et al., 2018). Pooled adjusted RRs indicated that smoking increases the risk of periodontitis (RR = 1.85 (95% CI [1.5, 2.2], $p < 0.05$). A meta-regression demonstrated that if smoking was eliminated in this population, the risk of periodontitis would be reduced by approximately 14%. Furthermore, data from a retrospective study about periodontal patients followed for 11 years suggested that heavy smokers (≥20 cigarettes/day) have a medium risk of disease progression than nonsmokers (OR = 5.9, 95% CI [1.6–21.3], $p = 0.007$) (Matuliene et al., 2008).

These results were confirmed by another prospective study by Costa and Cota (2019), who observed that the frequency of periodontal disease progression in smokers was 80%, whereas in nonsmokers it was almost twice as low with an OR of 4.98 (95% CI [1.78; 16.0], $p < 0.001$). There was also a significant dose–response relationship between pack-years of smoking and recurrent periodontitis, as well as a consistently better – albeit modest – treatment effect of periodontal flap surgery among nonsmokers versus smokers (Kotsakis et al., 2015). In smokers and nonsmokers, periodontal disease reduction ranged from 0.76 to 2.05 mm and 1.27 to 2.40 mm, respectively. In terms of clinical attachment level, the gains ranged from 0.29 to 1.6 mm and from 0.09 to 1.2 mm, respectively. In another study, the Bradford Hill criteria were used to comprehensively assess evidence that supported a causal association (Gelskey, 1999). The findings suggested that cigarette smoking is causally associated with periodontitis; that is, cigarette smoking was consistently associated with an increased prevalence/severity of periodontitis and was, on theoretical grounds, suspected of playing a causal role.

When comparing findings across studies, one should be cognizant that self-reported smoking status has been associated with underestimated smoking prevalence (Meng et al., 2011). Inaccuracy and mis-categorization may result in a biased estimation. Cotinine, an objectively measured smoking biomarker, provides a measure of recent nicotine exposure, including both active and passive smoking (Jarvis et al., 1987). Nicotine exposures within the same smoking category may

also differ according to the tobacco product, nicotine content, and inhalation technique (Benowitz, 1996). Smoking cessation advice has been suggested as a component of an overall oral health assessment by additionally addressing the social, financial and emotional issues. In addition to the general health benefits of stopping smoking upon the increased risk of oncologic, respiratory diseases, and circulatory disorders, there are other benefits that are directly linked with the oral environment (Souto et al., 2019).

In the literature, it has generally been noted that being a man carries an increased risk of periodontitis (Grossi et al., 1994). Data extracted from the NHANES indicate that men are more likely than women to suffer from periodontal conditions (56.4% vs. 38.4%) (Lipsky et al., 2021). This signifies a possible gender bias in the pathogenesis of the disease. Men are reported to have more severe periodontal disease when dental hygiene, age, socioeconomic status, and lifestyle are correlated with gender (Jain et al., 2020). A systematic study and MA evaluated gender-associated differences in periodontitis prevalence. The study identified a statistically significant relationship between gender and the prevalence of periodontitis, with a difference of 9% between men and women (37.4 vs. 28.1%; Jain et al., 2020). The results in **Chapter 5** support this finding, demonstrating that being male was significantly associated with a higher extent of periodontitis. The reason for this observation is usually attributed to lifestyle and less so to genetic factors (Bouchard et al., 2006).

A common observation in epidemiological studies is a loss of attachment being associated with increasing age (Eke et al., 2012a; Papapanou et al., 1991; Thomson et al., 2013b). It has been extensively reported that the prevalence and average severity of periodontitis increase with age for groups of individuals until virtually all middle-aged people have the disease (Timmerman & van der Weijden, 2006). Distinctive explanations have been proposed to describe the relationship between aging and periodontal tissue destruction. The "cumulative" hypothesis indicates that *"increased periodontal tissue destruction can be explained by chronic exposure to the effects of periodontitis"*. By contrast, the "age-related susceptibility" hypothesis poses that *"advancing age increases the risk of periodontitis through the dysregulation of the immune system"* (Hajishengallis, 2010). Several mechanistic studies have evaluated the role of changes that may involve both innate and acquired immunity (Hajishengallis 2010). Inflamm-aging refers to a chronically elevated and dysregulated inflammatory response that increases with age (Franceschi et al., 2000). The pathogenic processes responsible for the age-related increase in periodontal disease are not fully understood. As periodontal disease arises from a dysregulated or excessive host inflammatory response to subgingival microbial pathogens, it is reasonable to suggest that the dysregulated inflammatory response – characteristic of inflamm-aging – may contribute to the pathogenesis of periodontal disease. Furthermore, there is now

a greater recognition that multisystem conditions, such as frailty, play a crucial role in the well-being and health of an elderly populations. Frailty is defined as *"a clinically recognizable state of increased vulnerability, resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stressors is compromised"* (Xue, 2011). Similar to chronic diseases such as periodontal disease, the prevalence of frailty increases dramatically with increasing age. Furthermore, for many diseases, including oral conditions, the variation in occurrence explained by age seems larger than the variation explained by other known variables. Interestingly, the data presented in **Chapter 5** indicate that in the assessed periodontal population, age was related to the extent but not severity of adult periodontitis for people aged >55 years. In a cross-sectional study of 1,426 people aged 25–74 years, age was found to be the most highly correlated risk factor with ORs of 1.2 for those in the 35–44 age range and 9.01 for those in the 65–74 age range (Jain et al., 2020).

Summary and conclusions

This thesis aimed to investigate risk factors associated with periodontitis, including diabetes, smoking, and family history, by determining their prevalence among the periodontal population. The following primary research questions were addressed based on the evidence presented in the thesis:

- What is the prevalence of diabetes in a population of periodontitis patients in the Netherlands?
- What are the overall prevalence and odds of diabetes among subjects diagnosed with periodontitis compared with those without periodontitis?
- Is there a higher risk of tooth loss and edentulism among patients with diabetes compared with subjects without diabetes?
- What is the prevalence of smoking status, family aggregation, age, and gender among periodontitis patients in the Netherlands?

In the first chapter of the thesis, a retrospective study is presented that aimed to investigate the prevalence of diabetes in a population of periodontitis patients and to determine whether diabetes is associated with the severity and extent of periodontitis. Based on the outcomes of the periodontal practice-based study, this association was questioned in the sense that it appeared that patients with diabetes do not seem to be at greater risk of developing periodontitis, as assessed based on relative numbers of referred patients. Furthermore, the prevalence was lower than the national diabetes prevalence in the Netherlands. The findings do not seem to be in agreement with the conclusion of an SR in the existing literature, which found the overall prevalence and odds of having diabetes to be higher in periodontitis populations, as described **in the second chapter of the thesis**. However, the highest prevalence of diabetes among subjects with periodontitis was observed in studies conducted in Asia and the lowest in studies originating from Europe. With a reported diabetes prevalence of 4.3% among patients with periodontitis, the presumed association was also questioned as the prevalence of diabetes in Europe is approximately 10.3% among men and 9.6% among women aged 25 years and over (Global Burden of Disease Collaborative Network, 2020).

In the third and fourth chapters of the thesis, the aim was to comprehensively and critically evaluate the risk of tooth loss and edentulism among patients with diabetes relative to those without diabetes based on evidence from epidemiological studies. The existing literature reveals that moderate-certainty evidence exists for a small but significantly higher risk of tooth loss in patients with diabetes compared with those without diabetes. This was corroborated by the findings that weak evidence exists that among individuals diagnosed with diabetes, the prevalence of edentulism is higher than among those without diabetes. When the data were separated by the continent where the study was

performed, Asia and South America had numerically higher risks. With a potentially increased risk, patients with diabetes should receive special attention on factors related to tooth loss by dental care practitioners. Although the research presented in **Chapters 3** and **4** did not categorize data according to the causes of tooth loss, it did represent the true end-points – namely tooth loss and eventually edentulism – in relation to diabetes.

In the final chapter of the thesis, the prevalence of smoking and family aggregation in a population of periodontitis patients was investigated along with the association between these indicators (together with age and gender) and the severity and extent of periodontitis. According to our findings, smoking status, family aggregation, age, and gender are all factors associated with the extent and severity of adult periodontitis. More specifically, our results indicated that special preventive attention should be paid to subjects with a parent with periodontitis, as this was significantly associated with a larger extent of periodontitis. Generally, family history of periodontal health could be quickly and inexpensively assessed by clinicians to improve the prediction of patients' prognosis and preventive treatment need. Furthermore, in conjunction with the EFP S3 level clinical practice guideline of Treatment of Stage I–III periodontitis implementing tobacco smoking cessation interventions in patients undergoing periodontitis therapy is recommended (Herrera et al., 2022). To obtain an enhanced understanding of the implications of these findings, future research could address smoking cessation and the impact of education regarding the familial aggregation of periodontal disease.

Overall, considering all of the findings of this thesis, the risk assessment of our patients underpins the preventive oral care approach and must be individually tailored. Classification and diagnosis are distinct but linked entities, and the inclusion of established risk factors in the system will help to signpost the clinician and patient toward a more personalized approach to care provision.

The majority of the chapters in this thesis have already been published in scientific dental journals. As some of the studies concern a similar topic, there are inevitably considerable overlaps between chapters. Different journal requirements have also created some variations in terminology from one chapter to the next. For editorial reasons, the chapters in this thesis are not arranged chronologically.

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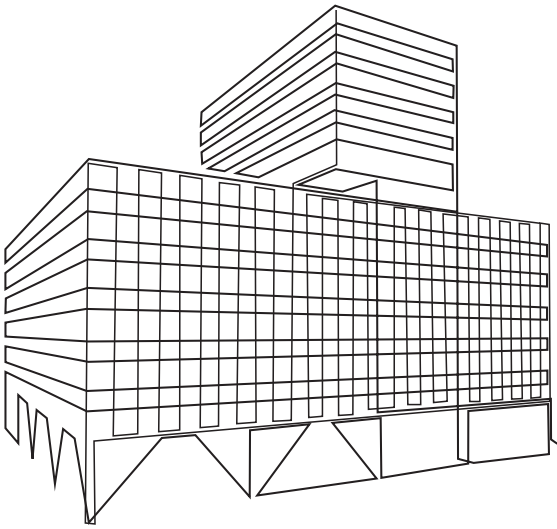

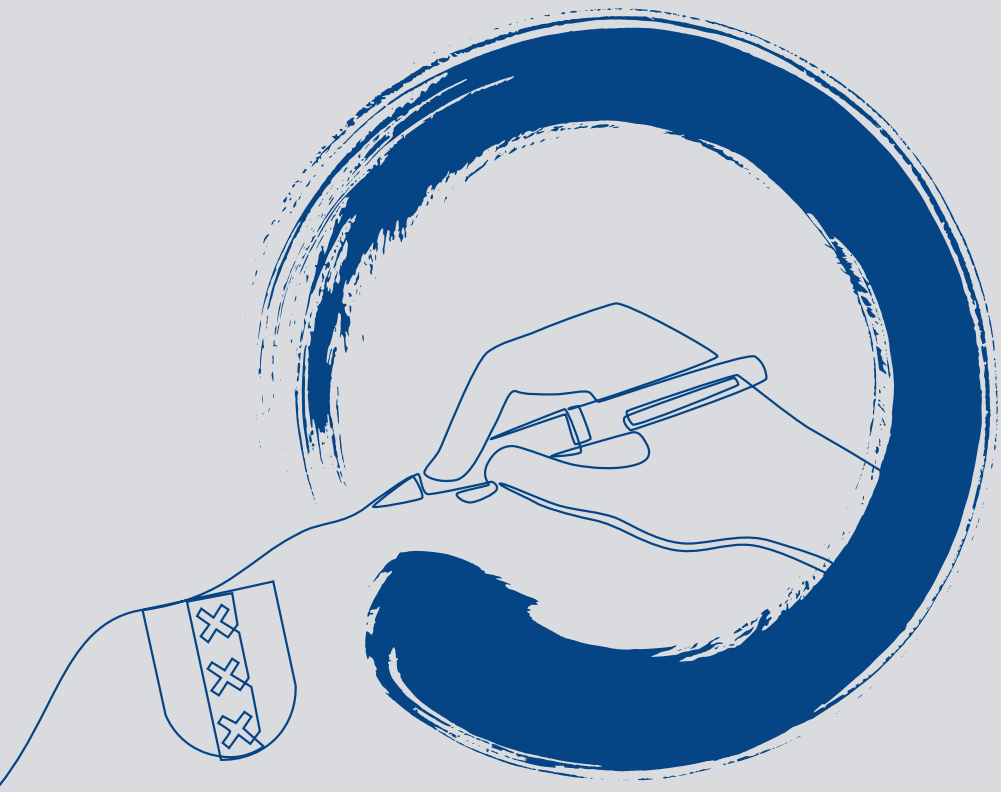

Nederlandse samenvatting voor leken

Risicofactoren van parodontitis: diabetes, roken en erfelijkheid

Tandplak bestaat hoofdzakelijk uit bacteriën. Een langdurige aanwezigheid van tandplak langs de tandvleesrand kan de zogenoemde parodontale gezondheid aantasten en een ontsteking van het tandvlees veroorzaken. In eerste instantie zal alleen de rand van het tandvlees ontstoken zijn; dan is er sprake van 'gingivitis'. Dit kan ongemerkt overgaan in een ontsteking die verder en samengaat met onherstelbaar verlies van kaakbot. Dit wordt 'parodontitis' genoemd. Dit is een chronische, multifactoriële ontsteking van de ondersteunende weefsels van de tanden en kiezen. Als dit onbehandeld blijft, kan het uiteindelijk leiden tot dusdanig verlies van de aanhechting van de tand of kies in het kaakbot dat deze mobiel worden en uiteindelijk verloren gaan. Omdat parodontitis is een van de belangrijkste oorzaken van gebitsverlies en wordt het beschouwd als bedreiging voor de mondgezondheid. De aandoening heeft een negatieve invloed op de kauwfunctie, de mogelijkheid tot eten, het gevoel van eigenwaarde, sociale acceptatie en levenskwaliteit.

De prevalentie van parodontitis varieert wereldwijd van 20% tot 50% en is volgens een overzicht van ziekten die mondiaal het meest voorkomen de zesde in de rij. De "ernstige" vorm van parodontitis wordt gerangschikt als de elfde meest voorkomende aandoening ter wereld. De Wereldgezondheidsorganisatie (WHO) ziet ernstige parodontitis daarom als een belangrijke mondziekte met een groeiende last waar naar schatting wereldwijd één miljard mensen aan lijden. De prevalentie van parodontitis is de afgelopen 25 jaar grotendeels ongewijzigd gebleven, ondanks de goede mondgezondheidszorg in Nederland en West-Europa. Parodontitis komt voor bij mensen van alle leeftijden, maar de prevalentie neemt geleidelijk toe met de leeftijd, met een incidentiepiek rond het 38e levensjaar. Gezien de ontwikkeling van de ernst van de ziekteprogressie met de leeftijd komt de aandoening het meest voor bij populaties van volwassen leeftijd en voornamelijk bij oudere patiënten. Dit komt door de cumulatieve effecten van langdurige blootstelling aan de vastgestelde risicofactoren. Er zijn al verschillende oorzakelijke factoren geïdentificeerd die het ontstaan en de progressie van parodontitis beïnvloeden. Tandplak op tanden en kiezen wordt beschouwd als een primaire oorzaak. Daarnaast zijn er risicofactoren die beïnvloed kunnen worden, zoals roken, slechte mondhygiëne, diabetes en hormonale veranderingen, maar ook niet-beïnvloedbare risicofactoren, zoals leeftijd en erfelijkheid. Inzicht in potentiële risicofactoren en de relatie tussen systemische ziekten en parodontale gezondheid zou kunnen helpen bij het herkennen van vatbare personen. Het signaleren van vatbare personen, bij voorkeur nog voor zij met parodontale aandoeningen te maken krijgen, zal het ontstaan en voortschrijden van de ontsteking helpen voorkomen. Dit zal van invloed zijn op de ontwikkeling van de

aandoening zoals uitgedrukt in mate en ernst.
In de wetenschappelijke literatuur bestaat er geen consensus over de definitie van de term 'risico'. Dit komt mede door de verschillen in wetenschappelijke disciplines die zich ermee bezighouden. Sommige definities gebruiken de termen van kansen dan wel waarschijnlijkheden, anderen van onzekerheid of verwachte waarden, aantal gebeurtenissen of juist gevolgen, of simpelweg doelstellingen. In de context van de geneeskunde wordt de term 'risico' gedefinieerd als de kans dat een gebeurtenis zich in de toekomst voordoet, zoals de kans dat een individu met een specifieke risicofactor een bepaalde ziekte ontwikkelt. Met betrekking tot medische risico's zijn er drie soorten variabelen van belang die als volgt worden ingedeeld. De eerste groep zijn risicofactoren of factoren die in verband zijn gebracht met een verhoogde kans op ziekte en waarvan wordt aangenomen dat ze een rol spelen in het ontstaan ervan. Een voorbeeld hiervan is iemands blootstelling aan een specifiek virus, zoals in de huidige tijd van corona en het omikronvirus en het risico op het ontstaan van COVID-19. De *tweede* groep bestaat uit risicodeterminanten; dit zijn achtergrondkenmerken die niet als oorzaak worden beschouwd en waar eventueel rekening mee kan worden gehouden, zoals leeftijd, geslacht en ras. Hierbij kan bijvoorbeeld worden gedacht aan de relatie tussen vrouwen en borstkanker en het feit dat ook mannen borstkanker kunnen ontwikkelen. De *derde* groep variabelen zijn risicovoorspellers. Deze worden gebruikt om iemands risico op een gebeurtenis te voorspellen, hetzij kwantitatief (aan de hand van een maat, zoals een cholesterolmeting om het risico op hart- en vaatziekten te bepalen), hetzij kwantitatief (door specifieke metingen of kwalitatief via een profiel met historische gegevens samen te stellen, zoals de familiegeschiedenis van een ziekte).

Diabetes mellitus (DM) is een chronische stofwisselingsstoornis die wordt gekenmerkt door verhoogde bloedglucosewaarden of hyperglykemie als gevolg van afwijkingen in de insulinesecretie. Diabetes, indien slecht gecontroleerd, wordt beschouwd als een risicofactor voor parodontitis. Het aantal mensen met de diagnose DM is de afgelopen decennia drastisch toegenomen, waardoor deze stoornis wereldwijd een van de meest uitdagende gezondheidsproblemen is geworden. In 2019 werd geschat dat ongeveer 463 miljoen volwassenen tussen 20 en 79 jaar aan DM lijdt, wat neerkomt op 9,3% van de wereldwijde volwassen bevolking. Schattingen laten zien dat dit aantal tegen 2030 zal stijgen tot 578 miljoen (10,2%) en rond 2045 tot 700 miljoen of 10,9% van de wereldwijde volwassen bevolking. Op basis van de oorzaak, het ontstaan, het ontwikkelen en het verloop wordt DM ingedeeld in verschillende typen. De meest voorkomende zijn type 1-diabetes mellitus (T1DM), type 2 diabetes mellitus

(T2DM) en zwangerschapsdiabetes. Ongeveer 5% tot 10% van de DM-patiënten heeft T1DM. Dit type stond voorheen bekend als insulineafhankelijke DM en wordt veroorzaakt door een verminderde insulineaanmaak. Belangrijke risicofactoren zijn genetische aanleg en omgevingstriggers zoals virale infecties. T2DM (90% tot 95% van de DM-gevallen), voorheen niet-insulineafhankelijke DM genoemd, wordt veroorzaakt door een afname van de respons van de lichaamscellen op insuline, wat bekend staat als insulineresistentie. T2DM wordt typisch geassocieerd met leefstijlfactoren zoals overgewicht en gebrek aan lichaamsbeweging, alsook met genetische factoren. Hoewel T2DM het vaakst voorkomt bij mensen boven de 45 jaar, stijgt het aantal kinderen, adolescenten en jongvolwassenen met deze vorm van diabetes als gevolg van toenemende obesitas, lichamelijke inactiviteit en ongezonde voedingspatronen. Niet goed ingestelde DM heeft nadelige gevolgen voor meerdere lichaamsorganen en verstoort de normale werking. Deze verstoring kan orgaanschade veroorzaken, met name aan de ogen, de nieren, het hart en de zenuwen.

Het ontstaan en de ernst van parodontitis zijn beide in verband gebracht met DM, waarbij wordt verondersteld dat er een 'tweezijdige 'relatie is tussen DM en parodontitis. Daarmee wordt bedoeld dat parodontitis een effect heeft op diabetes en dat diabetes ook een effect heeft op parodontitis. Studies hebben aangetoond dat het risico op parodontitis bij patiënten met niet goed ingestelde DM twee- tot driemaal zo groot is als bij patiënten met goed gecontroleerde DM. Hoewel de precieze mechanismen die ten grondslag liggen aan de relatie tussen DM en parodontitis niet volledig worden begrepen, zijn hiervoor meerdere factoren voorgesteld, waaronder het functioneren van het immuunsysteem en ontsteking. Studies hebben ook aangetoond dat chronische parodontitis en parodontale ontsteking patiënten met DM negatief kunnen beïnvloeden. Mensen met parodontitis blijken een hogere prevalentie van DM complicaties te hebben, zoals hart- en vaatziekten. Hoewel er veel wetenschappelijke literatuur bestaat over de risicofactoren die bijdragen aan beide ziekten en over de onderliggende biologische mechanismen, bespreekt de overgrote meerderheid van de artikelen de risicofactoren afzonderlijk in de context van parodontitis of DM. In het overzicht van risicofactoren voor zowel parodontitis als DM voorkomen de aanpasbare factoren roken, overgewicht, ongezonde voedingspatronen en levensstijl vaak voor. Verder zijn leeftijd, geslacht, ras en etniciteit, sociaaleconomische status, bepaalde systemische aandoeningen, genen, familiegeschiedenis van diabetescomplicaties en rookgeschiedenis de meest voorkomende niet-wijzigbare factoren.

Het onderzoek in **hoofdstuk 1** had als doel om de prevalentie van diabetes onder patiënten met parodontitis te evalueren en vast te stellen in hoeverre diabetes gerelateerd is aan de mate en ernst van parodontitis. In de retrospectieve studie werden gegevens gebruikt van patiënten die in een periode van 10 jaar waren

verwezen naar een gespecialiseerde kliniek voor parodontologie in Nederland. Patiënten kregen bij de intake een uitgebreid onderzoek naar specifieke kenmerken van parodontitis. Op basis van de klinische gegevens werden zij ingedeeld naar de mate en ernst van de parodontitis. Daarnaast werd op basis van zelfrapportage de aanwezigheid van diabetes geregistreerd. In totaal werden 5375 parodontitispatiënten met een gemiddelde leeftijd van 50 jaar geëvalueerd. De prevalentie van diabetes in deze patiëntengroep was 3,7%. Er kon geen verband worden vastgesteld tussen diabetes en de mate en ernst van parodontitis. De conclusie is dat de prevalentie van diabetes niet is gerelateerd aan de mate en/of de ernst van parodontitis. De diabetesprevalentie onder de parodontitispatiënten was lager dan de nationale diabetesprevalentie in Nederland.

Diabetes en parodontitis zijn beide complexe chronische ziekten met een veronderstelde tweezijdige relatie. Het onderzoek in **hoofdstuk 2** is een systematisch literatuuronderzoek naar de prevalentie en de kans op het hebben van diabetes bij personen met professioneel gediagnosticeerde parodontitis. Verschillende databases (MEDLINE-PubMed, CENTRAL en EMBASE) werden gericht doorzocht naar reeds gepubliceerde studies die deze vraag hadden onderzocht. De prevalentie van diabetes onder mensen met parodontitis werd geëxtraheerd of indien mogelijk berekend. Van de 803 onderzoeken die uit de zoekactie naar voren kwamen, voldeden 27 artikelen aan de vooropgestelde criteria. De prevalentie van diabetes was 13,1% bij mensen met parodontitis en 9,6% bij mensen zonder parodontitis. Op basis van sub analyse was de prevalentie van diabetes bij proefpersonen met parodontitis 6,2% wanneer diabetes zelf werd gerapporteerd, vergeleken met 17,3% wanneer diabetes professioneel werd vastgesteld. De hoogste prevalentie van diabetes bij mensen met parodontitis werd gerapporteerd in studies afkomstig uit Azië (17,2%) en de laagste in Europese studies (4,3%). De totale odds ratio voor patiënten met diabetes bij personen met parodontitis in vergelijking met degenen zonder parodontitis was 2,27 (95% CI [1,90;2,72]). Een aanzienlijke variatie in de definities en criteria van parodontitis werd waargenomen. Door het combineren van zelf gerapporteerde en professioneel vastgestelde diabetes en het ontbreken van stoorvariabelen voor diabetescontrole in de geïncludeerde studies trad vertekening op. De conclusies zijn dat de totale prevalentie en de kans op het hebben van diabetes hoger zijn bij parodontitispatiënten dan bij mensen zonder parodontitis. Zelf gerapporteerde diabetes onderschat de prevalentie in vergelijking met als dit professioneel werd vastgesteld, dat betekent dat bij zelfrapportage de prevalentie van diabetes lager dan bij professionele vaststelling. Verder werden geografische verschillen waargenomen, de hoogste diabetesprevalentie onder proefpersonen met parodontitis werd waargenomen in studies die in Azië werden uitgevoerd en de laagste werden geconstateerd in Europa.

Het systematisch literatuuronderzoek in **hoofdstuk 3** had als doel het risico

van gebitsverlies bij mensen met diabetes in vergelijking met mensen zonder diabetes te evalueren. In totaal werden 1087 studies gevonden in de databases. De screening en selectie op basis van vooraf opgestelde criteria resulteerde in 10 geschikte publicaties. Uit de beschrijvende analyse bleek dat 6 van deze studies wijzen op een significant hoger risico op gebitsverlies bij diabetespatiënten. Dit werd bevestigd door de meta-analyse waaruit bleek dat het relatief risico 1,63 was (95%CI [1,33;2,00] p< 0,00001). Uit de subgroep analyse kwam naar voren dat dit resultaat onafhankelijk was van de kwaliteitsbeoordeling van de studies. Het hogere risico van gebitsverlies bij diabetespatiënten was ook hoger wanneer alleen T2DM patiënten werden geanalyseerd. Patiënten met een slecht ingestelde diabetes vertoonden een significant hoger risico op gebitsverlies. Bij de analyse per werelddeel waar de studie werd uitgevoerd kwamen in Azië en Zuid-Amerika numeriek hogere risico's naar voren. Hierbij was sprake van een significant verschil met studies uitgevoerd in Europa en Noord-Amerika. De conclusie is dat er een matige zekerheid is voor een klein, maar significant hoger risico op gebitsverlies bij diabetespatiënten dan bij patiënten zonder diabetes.

Als alle tanden en kiezen verloren zijn geraakt, wordt gesproken van tandeloosheid. Hoofdstuk 5 vormde daarom de overtreffende trap van hoofdstuk 4. Het systematisch literatuuronderzoek in **hoofdstuk 4** had als doel het risico van tandeloosheid bij mensen met diabetes te evalueren in vergelijking met mensen zonder diabetes. Er werden 449 studies gevonden in de databases. De screening en selectie op basis van vooraf opgestelde criteria resulteerde in 6 publicaties die voldeden aan de geschiktheidscriteria. De grootte van de studies varieerde van 293 tot 15.943 deelnemers. De gegevens van alle 6 studies waren geschikt voor de meta-analyse. In totaal was 8,7% van de onderzochte mensen tandeloos. Van hen was gemiddeld 14,1% diabetespatiënt en 7,5% had geen diabetes. De totale odds ratio voor tandeloze diabetespatiënten in vergelijking met mensen zonder diabetes was 2,49 (95%CI: [1,75;3,54], P<0,00001). De conclusie was dat er een zwak bewijs is dat de prevalentie van tandeloosheid bij mensen met diabetes hoger is dan bij patiënten zonder diabetes.

Naast diabetes worden veelal leeftijd, geslacht, roken, genen en daarmee familiegeschiedenis beschouwd als de meest voorkomende niet-wijzigbare factoren zijn die van invloed kunnen zijn op parodontitis. Naast tandplak is roken is de bekendste risicofactor voor parodontitis. Leeftijd, geslacht en genetische kenmerken zijn risicodeterminanten, terwijl familiegeschiedenis wordt gezien als een risico voorspeller. Het onderzoek in **hoofdstuk 5** onderzocht de prevalentie van rokers en van parodontitis in de familie bij patiënten met professioneel gediagnosticeerde parodontitis. Daarbij werd ook onderzocht of deze factoren gerelateerd waren aan de mate en ernst van parodontitis. In de retrospectieve studie werden gegevens gebruikt van patiënten die in een periode van 10 jaar waren verwezen naar een gespecialiseerde kliniek voor parodontologie in

Nederland. Zij kregen bij de intake een uitgebreid onderzoek naar specifieke kenmerken van parodontitis. Op basis van de klinische gegevens werden patiënten ingedeeld naar de mate en ernst van de parodontitis. Ook werden gegevens over de leeftijd, familiegeschiedenis van parodontitis en rookstatus geregistreerd. In totaal werden 5375 parodontitispatiënten met een gemiddelde leeftijd van 50 jaar geëvalueerd. De prevalentie van roken in deze patiëntengroep was 34% en 37% van de parodontitispatiënten had ten minste één een ouder of broer of zus met parodontitis. De kans op ernstige parodontitis was groter als de patiënt een man was, rookte of een broer met parodontitis had. Man zijn, roken en een ouder met parodontitis waren significant geassocieerd met een grotere mate van parodontitis. De conclusie is dat in de onderzochte volwassenenpopulatie de familiaire relaties met parodontitis, rookstatus, leeftijd en geslacht factoren zijn die verband houden met de hoeveelheid en ernst van parodontitis.

Algemene conclusie

Het onderzoek in dit proefschrift had ten doel om risicofactoren voor parodontitis, waaronder diabetes mellitus, roken en familiegeschiedenis te evalueren. Dit naast literatuuronderzoek ook door de prevalentie van deze factoren bij de grote populatie patiënten met parodontitis te bepalen. De meeste hoofdstukken richten zich op het verband tussen parodontitis en diabetes.
Op basis van de uitkomsten van de studie in de Nederlandse parodontologiepraktijk wordt deze associatie in twijfel getrokken. Zoals beoordeeld op basis van het aantal verwezen patiënten lijken mensen met diabetes geen groter risico te hebben op het ontwikkelen van parodontitis. Deze bevinding lijkt niet in overeenstemming te zijn met de conclusie van een systematische review van de bestaande gepubliceerde literatuur, waarin werd vastgesteld dat de totale prevalentie en de kans op het hebben van diabetes hoger is bij parodontitispatiënten. De hoogste prevalentie van diabetes onder mensen met parodontitis werd echter voornamelijk waargenomen in studies uitgevoerd in Azië. De diabetesprevalentie onder patiënten met parodontitis in Europa was echter 4,3% wat wel bijdraagt aan twijfels over het veronderstelde verband. In Europa is bij mensen van 25 jaar en ouder de prevalentie van diabetes namelijk ongeveer 10,3% bij mannen en 9,6% bij vrouwen. Op basis van de reeds gepubliceerde literatuur blijkt er een matige zekerheid te zijn voor een klein, maar significant hoger risico op gebitsverlies bij diabetespatiënten in vergelijking met mensen zonder diabetes. Dit wordt verder ondersteund door het gevonden zwakke bewijs dat de prevalentie van tandeloosheid hoger is bij mensen met diabetes dan bij patiënten zonder diabetes. Gezien dit verhoogde risico zouden patiënten met diabetes speciale aandacht van de mondzorgverleners moeten krijgen voor de preventie van tandbederf (cariës) en tandvleesontsteking (parodontitis). Uit de retrospectieve analyse van volwassen patiënten met parodontitis die naar een Nederlandse parodontologiepraktijk werden verwezen komt naar voren dat de familiegeschiedenis, roken, leeftijd en geslacht factoren zijn die verband houden met de mate en ernst van parodontitis. De resultaten wijzen erop dat speciale preventieve aandacht moet worden besteed aan personen met een ouder met parodontitis, aangezien dit significant geassocieerd is met een hogere mate van parodontitis.
Over het geheel genomen dragen de bevindingen van dit proefschrift bij aan de veronderstelling dat de risicobeoordeling van de parodontitispatiënt ten grondslag ligt aan de preventieve mondzorg en dat deze individueel moet worden afgestemd. De integratie van de vastgestelde risico's in de parodontale behandeling helpt zowel de mondzorgverlener als de patiënt om een meer gepersonaliseerde aanpak mogelijk te maken en daarmee de zorgverlening te verbeteren.

Galbūt ne garsas skambės tyloj,

o tyla garse?

Perhaps it is not the sound

in the silence

but the silence in the sound?

Andrius Mamontovas

Santrauka lietuvių kalba

Periodontito rizikos veiksniai – diabetas, rūkymas ir paveldimumas

Dantų apnašos – gali būti apibūdinamos kaip minkštos sankaupos, sudarančios prie danties ar kitų kietų paviršių, esančių burnoje, prilipusią bioplėvelę, kurios pagrindinė sudėtis – bakterijos. Ilgalaikis apnašų buvimas palei dantenų liniją gali paveikti apydančio audinių sveikatą ir sukelti dantenų uždegimą – gingivitą. Tokiu atveju dantenos būna paraudusios, paburkusios, kraujuoja, kartais skauda. Gingivitas yra lengva apydančio audinių liga, kuri lengvai išgydoma bei kontroliuojama laikantis puikios kasdienės asmeninės burnos higienos ir reguliariai lankantis pas burnos higienistą. Negydomas gingivitas ilgainiui progresuoja į periodontitą – dantį supančių atraminių audinių (kaulo, raiščių) uždegimą ir vėliau - praradimą. Deja, šis procesas yra negrįžtamas. Gingivitą galima išgydyti: apydantyje pokyčių nelieka, o periodontito sukelti pažeidimai yra negrįžtami. Periodontito gydymo dėka ligą galima stabdyti, kad liga neprogresuotų. Periodontitas yra sunkesnė apydančio ligos forma nei gingivitas. Pirmiausia uždegimas prasideda dantenose, vėliau, jam išplitus ir užsitęsus, pažeidžia dantį prilaikantį raištį, kuris supa kaulą. Nekontroliuojama ligos eiga lemia dantų atramos netekimą ir paslankumą, vėliau – ir iškritimą. Periodontitas yra viena iš pagrindinių dantų netekimo priežasčių, todėl jis sukelia didelę grėsmę burnos sveikatai. Ši būklė turi neigiamos įtakos kramtymo funkcijai, gebėjimui valgyti, savigarbai, socialiniam pripažinimui ir gyvenimo kokybei.

Pasaulyje nustatomas 20–50 proc. populiacijos periodontito paplitimas. Tarp ligų, kurių paplitimas pasaulyje didžiausias, ji yra šešta pagal dažnumą. Sunkaus laipsnio periodontitas yra 11-oji pagal paplitimą liga pasaulyje. Pasaulio sveikatos organizacija (PSO) sunkaus laipsnio periodontitą laiko pagrindine burnos ertmės liga, kurios paplitimas vis didėja ir kuria, kaip manoma, serga milijardas žmonių. Pasaulyje periodontito paplitimas iš esmės išliko nepakitęs. Deja, ir Nyderlanduose, ir bendrai Vakarų Europoje, nors pastarosios šalyse yra gera burnos sveikatos priežiūra. Periodontitas atsiranda įvairaus amžiaus žmonėms, tačiau jo paplitimas pamažu didėja metams bėgant. Dažniausiai liga pirmą kartą nustatoma asmenims apie 38-uosius metus. Šį procesą lemia kumuliacija: žmogaus amžius kartu su ilgalaikiu rizikos veiksnių poveikiu.

Yra nustatyti skirtingi priežastiniai veiksniai, lemiantys periodontito atsiradimą ir progresavimą. Bakterinės dantų apnašos yra laikomos pagrindine ligos priežastimi. Dar yra dviejų grupių rizikos veiksniai: 1. *žmogaus lemiami*, pvz.: rūkymas, prasta burnos higiena, diabetas; 2. *žmogaus nelemiami*, pvz., amžius, lytis ir paveldimumas. Atsižvelgus į galimus rizikos veiksnius ir į periodontito bei bendros sveikatos sąsają, galima nustatyti asmenis, kurie gali būti imlūs periodontitui. Svarbu šiuos asmenis nustatyti dar prieš jiems susergant periodontitu ir, pasitelkiant edukaciją, užkirsti kelią ligai atsirasti arba ja sergant – toliau progresuoti. Mokslo literatūroje nėra bendros nuomonės dėl termino „rizika“ apibrėžties.

Nuomonių neatitiktį iš dalies lemia rizikas nagrinėjančio mokslo metodikų ir disciplinų skirtumai. Apibrėžtyse vartojami skirtingi terminai: vienur šansų santykis arba tikimybė, kitur – neapibrėžtumas arba tikėtina vertė, dar kitur – įvykių arba padarinių skaičius arba tiesiog tikslai.

Medicinos srityje rizika apibrėžiama kaip tikimybė, kad ateityje bus toks įvykis, pvz., tikimybė, kad tam tikrą rizikos veiksnį turintis asmuo susirgs tam tikra liga. Medicinoje rizika skirstoma į tris pagrindines grupes. Pirmoji grupė – tai *rizikos veiksniai* arba *veiksniai, susiję su padidėjusia ligos rizika.* Manoma, kad jie turi tiesioginės įtakos ligai atsirasti. Pavyzdys – asmens sąlytis su tam tikru virusu, pvz., su Corona virusu, ir rizika susirgti COVID-19. Antrąją grupę sudaro *lemiamieji veiksniai.* Tai aplinkos charakteristikos, kurios nėra laikomos pirmine priežastimi, jų neįmanoma paveikti, tačiau į jas reikia atsižvelgti, pvz., amžių, lytį ir rasę. Trečioji kintamųjų grupė yra *prognoziniai rizikos veiksniai.* Jie naudojami siekiant numatyti asmens riziką remiantis kiekybiniais (pvz., cholesterolio kiekis širdies ir kraujagyslių ligų rizikai nustatyti) arba kokybiniais (konkretūs duomenys vertinant bendrųjų duomenų profilį, pvz., šeimos ligos istorija) tyrimais, metodais, kintamaisiais, požymiais.

Cukrinis diabetas (toliau – diabetas) yra sunki liga, sukelianti didesnį nei įprastai cukraus kiekį kraujyje. Diabetas atsiranda, kai kūnas negali pasigaminti arba efektyviai panaudoti savo insulino – hormono, kurį gamina specialios kasos ląstelės, vadinamos salelėmis. Diabetas, jei blogai valdomas, laikomas periodontito rizikos veiksniu. Žmonių, kuriems diagnozuotas diabetas, nuolat daugėja, todėl šis liga yra viena iš aktualiausių sveikatos problemų. Apskaičiuota, kad 2019 m. apie 463 mln. 20–79 metų amžiaus suaugusiųjų serga diabetu, o tai sudaro 9,3 proc. visų pasaulio suaugusiųjų. Apytiksliais apskaičiavimais prognozuojama, kad šis skaičius padidės iki 578 milijonų (10,2 proc.), o apie 2045 m. – iki 700 milijonų, arba 10,9 proc. pasaulio suaugusiųjų.

Pagal priežastį, išsivystymą ir progresavimą diabetas yra skirstomas į kelis tipus. Dažniausiai nustatomas *1 tipo diabetas, 2 tipo diabetas* ir *nėščiųjų diabetas.* Apie 5–10 proc. diabetu sergančių žmonių turi 1 tipo cukrinio diabeto formą. Šis tipas anksčiau buvo žinomas kaip nuo insulino priklausomas diabetas, kurį sukelia sutrikusi insulino gamyba. Svarbūs rizikos veiksniai yra genetinis polinkis ir aplinkos veiksniai, pavyzdžiui, virusinės infekcijos. 2 tipo diabetą (90–95 proc. sergančių žmonių), anksčiau vadintą nuo insulino nepriklausomu, sukelia sumažėjęs organizmo ląstelių atsakas į insuliną, t. y. atsparumas insulinui. Šio tipo diabetas dažniausiai yra susijęs su gyvensenos veiksniais, pvz., nutukimu ir nejudra, taip pat su genetiniais veiksniais. Jis yra labiausiai paplitęs ir dažnai nustatomas vyresniems nei 45 metų žmonėms, tačiau vaikų, paauglių ir jaunų suaugusiųjų, sergančių šia diabeto forma, skaičius vis auga dėl didėjančio

nutukimo, nejudros ir nesveikos mitybos. Netinkamai sureguliuotas diabetas daro neigiamą poveikį daugeliui kūno organų ir sutrikdo normalią organizmo funkciją, todėl šių procesų padarinys – sutrikusi akių, inkstų, širdies ir nervų sistemos veikla.
Remiantis epidemiologiniais tyrimais, sergant diabetu rizika atsirasti apydančio ligai padidėja apytiksliai tris kartus ir ši liga laikoma viena iš periodontito atsiradimo rizikos veiksnių. Periodontito sunkumas, sergant diabetu, priklauso nuo ligos trukmės bei gliukozės kiekio kraujyje kontrolės. Kai kurių klinikinių tyrimų duomenimis, sergant diabetu, periodontito gydymo rezultatai taip pat būna blogesni negu tų, kurių gliukozės kiekis kraujyje gerai kontroliuojamas.
Periodontito atsiradimas ir ligos sunkumas yra susiję su diabetu: daroma prielaida, kad šios dvi ligos turi abipusį ryšį. Vadinasi, periodontitas turi įtakos diabetui, o diabetas – periodontitui. Tikslūs mechanizmai, kuriais grindžiamas ryšys tarp diabeto ir periodontito, nėra visiškai aiškūs, tačiau buvo nustatyta keletas veiksnių, lemiančių šią sąsają, t. y. imuninės sistemos funkcionavimas ir uždegimas. Tyrimais nustatyta, kad lėtinis periodontitas gali neigiamai paveikti pacientų, sergančių diabetu, sveikatos būklę, pvz., daugiau pasireiškusių komplikacijų. Šiuo metu yra daug mokslo literatūros apie rizikos veiksnius, lemiančius abiejų ligų atsiradimą ir jas pagrindžiančius biologinius mechanizmus, tačiau daugiausia straipsniuose periodontito arba diabeto rizikos veiksniai aptariami atskirai. Apibendrinus, tiek periodontito, tiek diabeto bendri rizikos veiksniai skirstomi: į *valdomuosius:* rūkymas, nutukimas, nesveika mityba, nesveika gyvensena; ir *nevaldomuosius:* amžius, lytis, rasė ar etninė aplinkybė, socialinis ir ekonominis statusas, tam tikros sisteminės ligos, genai, šeimos diabeto komplikacijų anamnezė.

1 skyriuje aprašytu tyrimu siekta įvertinti diabeto paplitimą tarp periodontitu sergančių pacientų ir nustatyti, ar diabetas susijęs su periodontito išplitimo ir sunkumo laipsniu. Atliekant retrospektyvųjį tyrimą buvo naudojami pacientų, kurie per 10 metų buvo siunčiami į specializuotą Nyderlandų periodontologijos kliniką dėl periodontito gydymo, duomenys. Pacientams buvo atliktas išsamus apydančio ligos tyrimas – klinikiniai uždegimo apimtų dantenų matavimai. Remiantis surinktais duomenimis, pacientai buvo skirstomi pagal periodontito išplitimo ir ligos sunkumo laispnį – pagal prof. dr. Ubele'ą van der Veldeną periodontito sudarytą klasifikaciją. Be to, iš pacientų anketos buvo surinkta informacija apie diabetą . Iš viso buvo ištirta 5375 periodontitu sergantys pacientai, kurių vidutinis amžius buvo 50 metų. Diabeto paplitimas šioje pacientų grupėje buvo **3,7** proc. Atlikus statistinius tyrimus, statistiškai reikšmingo ryšio tarp diabeto ir periodontito išplitimo ir ligos sunkumo laipsnio **nenustatyta.** Apibendrinant galima prieiti prie išvados, kad tirtos populiacijos diabeto paplitimas nesusijęs su periodontito išplitimu ir (arba) sunkumu. Šalia to, tyrime nustatytas diabeto paplitimas tarp periodontitu sergančių pacientų buvo mažesnis, nei nacionalinis diabeto paplitimas Nyderlanduose.

Diabetas ir periodontitas yra sudėtingos kompleksinės lėtinės ligos, susijusios abipusiu santykiu. **2 skyriuje** pristatytas tyrimas yra sisteminė literatūros apie diabeto paplitimą ir tikimybę diabetu susirgti pacientams, kuriems periodontitą diagnozavo burnos priežiūros specialistas, apžvalga. Keliose duomenų bazėse (MEDLINE-PubMed, CENTRAL ir EMBASE) buvo ieškoma jau paskelbtų tyrimų, kuriuose buvo nagrinėjamas šis klausimas. Diabeto paplitimo duomenys tarp žmonių, sergančių periodontitu, buvo paimti iš originalių publikacijų arba, jeigu įmanoma, buvo apskaičiuoti literatūros apžvalgos autorių. Iš 803 paieškos metu gautų tyrimų, pagal iš anksto nustatytus kriterijus, paiešką atitiko 27 straipsniai. Rezultatai parodė, jog diabeto paplitimas buvo **13,1** proc. tarp žmonių, sergančių periodontitu, ir **9,6** proc. tarp žmonių, nesergančių periodontitu. Remiantis subanalizėmis buvo nustatyta, kad diabeto paplitimas tarp asmenų, sergančių periodontitu, buvo **6,2** proc., jei cukrinis diabetas buvo nustatytas pagal subjektyvius paciento pateiktus duomenis, palyginti su **17,3** proc., jei diabetas buvo nustatytas laboratoriškai. Pagal geografinį pasiskirstymą, didžiausias cukrinio diabeto paplitimas tarp periodontitu sergančių asmenų buvo Azijoje (**17,2** proc.), o mažiausias – Europoje (**4,3** proc.).
Bendras diabetu sergančių asmenų šansų santykis, palyginti su periodontitu sergančių ir neturinčių periodontito asmenų, buvo **2,27** (95% CI [1,90;2,72]). Vadinasi, žmonės, sergantys periodontitu, turi 2,27 karto didesnę galimybę sirgti diabetu, nei periodontitu nesergantys žmonės.

3 skyriuje pateiktoje sisteminėje literatūros apžvalgoje buvo siekiama įvertinti dantų netekimo riziką diabetu sergantiems pacientams, palyginti su diabetu nesergančiais žmonėmis. Keliose duomenų bazėse (MEDLINE-PubMed, CENTRAL ir EMBASE) buvo ieškoma jau paskelbtų tyrimų, kuriuose buvo nagrinėjamas šis klausimas. Iš viso duomenų bazėse buvo rasti 1087 tyrimai. Pagal iš anksto nustatytus kriterijus atrinkta 10 sisteminei apžvalgai tinkamų publikacijų. Remiantis aprašomąja analize, 6 iš analizuotų tyrimų nustatyta, kad dantų netekimo rizika yra didesnė cukriniu diabetu sergantiems pacientams. Tai patvirtino ir metaanalizė, kuri parodė, kad santykinė rizika buvo **1,63** (95% CI [1,33;2,00] p < 0,00001). Pacientams, kurių diabetas buvo blogai valdomas, buvo nustatyta reikšmingai didesnė dantų netekimo rizika. Atsižvelgiant į žemyną, kuriame buvo atliktas tyrimas, Azijoje ir Pietų Amerikoje buvo nustatyta daug didesnė rizika.

Visų dantų netekimas vadinamas bedantysite, todėl **4 skyriuje** yra papildoma **3 skyriaus** medžiaga. **4 skyriuje** pateiktoje sistemingos literatūros apžvalgoje buvo siekiama įvertinti diabetu sergančių žmonių dantų netekimo (bedantystės) riziką ir palyginti ją su diabeto neturinčiais žmonėmis. Duomenų bazėse rasti 449 atlikti tyrimai. Pagal iš anksto nustatytus kriterijus buvo atrinkti 6 tyrimai, kurių duomenys buvo tinkami metaanalizei atlikti. Iš viso **8,7** proc. tirtų žmonių buvo bedančiai. Iš jų vidutiniškai **14,1** proc. žmonių sirgo diabetu, o **7,5** proc. neturėjo diabeto. Diabetu

sergantiems žmonėms, palyginti su diabetu nesergančiais pacientais, bendrasis bedantystės šansų santykis buvo **2,49** (95%CI: [1,75;3,54], P < 0,00001). Vadinasi, sergant diabetu, šansas turėti bedantystę buvo 2,49 kartų didesnis nei tų, kurie neturi diabeto.

Be diabeto, amžius, lytis, rūkymas, genai ir periodontito šeimos istorija yra svarbiausi veiksniai, laikomi dažniausiais nelemiamaisiais veiksniais, galinčiais turėti įtakos periodontitui. Šalia bakterinių apnašų, rūkymas yra geriausiai žinomas periodontito rizikos veiksnys. Lemiamieji veiksniai yra amžius, lytis ir genetinės savybės, o šeimos istorija laikoma rizikos prognozavimo žymeniu. **5 skyriuje** pateiktas tyrimas ištyrė rūkymo paplitimą ir periodontito šeimoje paplitimą tarp pacientų, sergančių periodontitu. Taip pat buvo nagrinėjama, ar šie veiksniai buvo susiję su periodontito išplitimo ir sunkumo laipsniu. Retrospektyviajame tyrime buvo naudojami pacientų, kaip ir **1 skyriuje**, kurie per 10 metų buvo siunčiami į specializuotą Nyderlandų periodontologijos kliniką dėl periodontito gydymo, duomenys. Taip pat buvo surinkti duomenys apie amžių, šeiminę periodontito anamnezę ir rūkymą. Iš viso buvo tiriami 5375 periodontitu sergantys pacientai, kurių vidutinis amžius – 50 metų. Rūkymo paplitimas šioje pacientų grupėje buvo **34** proc. **37** proc. periodontitu sergantys pacientai turėjo bent vieną periodontitu sergantį tėvą arba brolį ar seserį. Tikimybė, kad bus diagnozuotas sunkus periodontito laipsnis, buvo didesnė, jei pacientas buvo vyras, rūkė arba turėjo brolį, sergantį periodontitu. Vyriškoji lytis, rūkymas ir vienas iš tėvų, sergančių periodontitu, buvo statistiškai reikšmingai susiję su didesniu periodontito laipsniu. Apibendrinant galima teigti, kad ištirtosios suaugusiųjų populiacijos šeimos ryšiai su periodontitu sergančiu žmogumi, rūkymas, amžius ir lytis yra veiksniai, susiję su periodontito išplitimu ir laipsniu.

Bendra išvada

Šios disertacijos darbo tikslas – įvertinti periodontito rizikos veiksnius, įskaitant diabetą, rūkymą ir šeiminę periodontito anamnezę. Taip pat atlikta literatūros apie rizikos veiksnių paplitimą didelėje periodontitu sergančių pacientų populiacijoje apžvalga, pagrindinis dėmesys skirtas periodontito ir diabeto sąsajai.

Remiantis tyrimais, atliktais pagal Nyderlandų specializuotos periodontologijos klinikos duomenis, periodontito ir diabeto sąsaja, tiksliau jos stiprumu, buvo suabejota. Šie pacientai buvo specialiai siųsti periodontologiniam gydymui. Tad tai buvo tikslinė populiacija: šiems pacientams galima tikėtis nustatyti periodontito ir diabeto sąsajos stiprumą. Atsižvelgiant į gautus rezultatus, daroma išvada – diabetu sergantys žmonės neturi didesnės rizikos susirgti periodontitu.

Ši išvada neatitinka sisteminės literatūros apžvalgos rezultatų, kur nustatyta, kad diabeto paplitimas bei žmonių, turinčių periodontitą, susirgti diabetu tikimybė yra didesnė. Svarbu paminėti, kad didžiausias diabeto paplitimas tarp periodontitu sergančių žmonių buvo daugiausia pastebėtas Azijoje atliktuose tyrimuose. Diabeto paplitimas tarp periodontitu sergančių pacientų Europoje buvo 4,3 proc., o tai verčia abejoti dėl periodontito ir diabeto sąsajos stiprumo. Įdomu atkreipti dėmesį, jog bendroje Europos populiacijoje tarp 25 metų ir vyresnių žmonių diabeto paplitimas yra apie 10,3 proc.; tarp vyrų ir 9,6 proc. tarp moterų. Šiuos teiginius patvirtina statistiškai silpni įrodymai, kad bedantystės paplitimas yra didesnis tarp sergančių nei nesergančių cukriniu diabetu žmonių.

Atsižvelgiant į šią padidėjusią riziką, diabetu sergantiems pacientams turėtų būti pabrėžiamos ir skiriamos burnos sveikatos priežiūros paslaugos – būtent dantų ėduonies (karieso) ir apydančio ligų (gingivito ir periodontito) profilaktikai.

Tirti suaugę pacientai, sergantys periodontitu, kurie buvo siųsti į specializuotą Nyderlandų periodontologijos kliniką. Tyrimas parodė, kad periodontito šeimos istorija, rūkymas, amžius ir lytis yra veiksniai, susiję su periodontito išplitimu ir ūmumu. Rezultatai rodo, kad ypatingą profilaktinį dėmesį reikėtų skirti asmenims, kurių vienas iš tėvų serga periodontitu, nes tai yra susiję su sunkesne periodontito ligos forma.

Apskritai šio darbo išvados prisideda prie prielaidos, kad periodontitu sergančio paciento rizikos vertinimas yra profilaktinės burnos priežiūros pagrindas ir kad ji turėtų būti individualiai pritaikyta kiekvienam pacientui. Nustatytų rizikos veiksnių įtraukimas į periodontologinį gydymą padeda ir burnos priežiūros specialistui, ir pacientui – galima individualizuoti vertinimą ir taip pagerinti priežiūros paslaugų teikimą.

Addenda:

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List of frequently used abbreviations

About the author (Biography & PhD portfolio)

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Chapter 1

Prevalence of diabetes among patients diagnosed with periodontitis: A retrospective cross-sectional study.

Ziukaite L, Slot DE, Cobb CM, Coucke W, Van der Weijden GA.

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Ziukaite contributed to design, analysis and interpretation and drafted the manuscript. Slot contributed to conception and design, analysis and interpretation and critically revised the manuscript. Cobb contributed to analysis and interpretation and critically revised the manuscript. Couke contributed to statistical analysis and interpretation and critically revised the manuscript. 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.
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Chapter 2

Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies.

Ziukaite L, Slot DE, Van der Weijden FA.

J Clin Periodontol. 2018 Jun;45(6):650-662.
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Ziukaite, first author, contributed to the design, contributed to acquisition, analysis and interpretation, and drafted manuscript; Slot contributed to the conception and design, contributed to acquisition, analysis and interpretation, and drafted manuscript; Van der Weijden, overall supervisor, contributed to conception and design, contributed to acquisition, analysis and interpretation, and critically revised manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.
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Chapter 3

The risk of tooth loss in patients with diabetes: A systematic review and meta-analysis.

Weijdijk LPM, Ziukaite L, Van der Weijden GAF, Bakker EWP, Slot DE.

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Chapter 4

Edentulism among diabetic patients compared to non-diabetic controls: A systematic review and meta-analysis.

Ziukaite L, Weijdijk LPM, Tang J, Slot DE, Van der Weijden GA.

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Ziukaite: contributed to search and selection, analysis and interpretation, and critically drafted the manuscript. Weijdijk: contributed to the design, search and selection, quality assessment, analysis and interpretation of data, and critically revised the manuscript. Tang: contributed to the design, analysis and interpretation of data and helped draft the manuscript. Slot: contributed to to conception and design, analysis and interpretation, and critically revised the manuscript. 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.
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Chapter 5

Family history of periodontal disease and prevalence of smoking status among adult periodontitis patients: a cross-sectional study.

Ziukaite L, Slot DE, Loos BG, Coucke W, Van der Weijden GA.

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List of frequently used abbreviations

ACTA	Academic Centre for Dentistry Amsterdam
AAP	American Academy of Periodontology
BOP	Bleeding On Probing
CAL	Clinical Attachment Level
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CM	Diabetes mellitus was diagnosed in a clinical setting
CPI	Community Periodontal Index
CPITN	Community Periodontal Index of Treatment Needs
DM	Diabetes Mellitus
DMFT	Decayed Missing Filled Teeth
DMR	Dental/Medical Record
DR	Dental Records
E	Edentulousness
EFP	European Federation of Periodontology
EMA	European Medicines Agency
EMBASE	Excerpta Medica Database
F	Females
FDI	World Dental Federation
FPG	Fasting Plasma Glucose
HbA1c	Glycated hemoglobin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Helsinki Aging study
HCHS/SOL	Hispanic Community Health Study / Study of Latinos
IDF	International Diabetes Federation
INT	Interview
KNHANES	Korea National Health and Nutrition Examination Survey
LOA	Loss Of Attachment
M	Males
MA	Meta-Analysis
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
N	the total Number
n	Numbers of participants in the subgroups
n/a	unknown/not applicable
NFBC	Northern Finland Birth Cohort
NHANES	The National Health and Nutrition Examination Survey
NOS	Newcastle-Ottawa Scale
OHRQoL	Oral Health Related Quality of Life
OR	Odds Ratio

PD	Professionally Diagnosed
PECOS	Population, Exposure, Comparator, Outcome
PPD	Probing Pocket Depth
PMT	Periodontal Maintenance Therapy
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PrDM	Previously known Diabetes Mellitus
ProfD	Professionally Diagnosed
PROSpECT	Periodontal Research on Multimorbidity and Systemic Health Clinical Study Group and Research Consortium
Q	Questionnaire
QoL	Quality of Life
RCT	Randomized Clinical Trial
RECORD	Reporting of studies Conducted using Observational Routinely-collected Data
RoB	Risk of Bias
ROBINS E	Risk Of Bias In Non-randomized Studies of Exposure
RR	Risk Ratio
ScDM	Screening detected Diabetes Mellitus
SD	Standard Deviation
Self R	Self Reported
SHIP	Study of Health In Pomerania
SR	Systematic Review
SR	(chapter 2, chapter 4 table 1) information about diabetes was Self-Reported
sRR	summary Relative Risk
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T	missing Teeth
T+	present Teeth
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UvA	University of Amsterdam
VU	Vrije Universiteit Amsterdam
WHO	World Health Organization

Laura
Žiūkaitė

Biography

Laura's appreciation and love for dentistry can be traced back to the 1990s. As a young child, she would put on an oversized white lab coat to assist her uncle Saulius in his dental practice in the small western town of Lithuania, Mažeikiai in Lithuania. Playing a young "dentist" by her uncle's chairside through the years amalgamated what she loved to do - which is take care of people while engaging her hands and her intellect.

In 2009 Laura graduated from the Lithuanian University of Health Sciences (formerly known as Kaunas Medicine University) with a Master's degree in dentistry. Early in her clinical practice, it became evident that she wanted to pursue further studies in the field of Periodontics. After two years of practice as a general dentist, Laura was accepted to the postgraduate master's program in Periodontology and Implant Dentistry at the Academic Center of Dentistry Amsterdam (ACTA), the Netherlands.

The beginning of her research life started during her specialty studies when she wrote a scientific thesis that was compulsory to fulfill the program's requirements. The chosen topic concerned the prevalence of risk factors among periodontitis patients, supervised by Prof. Dr. Dagmar Else Slot and Prof. Dr. Fridus van der Weijden. She graduated in 2015 from the European Federation of Periodontology (EFP) accredited program.

From 2017 Laura was working in the multidisciplinary team of the 'Praktijk voor Parodontologie en Implantologie Arnhem' (PPIA). Along with the clinical work, she continued her studies and focus on risk factors for periodontitis, at the department of Periodontology at ACTA.

In 2019 her biggest masterpiece arrived. Laura became a mother to Vincent Antanas Nilesh. In 2021, during the Covid-19 pandemic, Laura and her son moved back to her home country Lithuania. Currently, they both live in Vilnius, the capital

of Lithuania. However, you may still run into them on the streets of Amsterdam as they come and visit the Netherlands often.
Today Laura works as a periodontist at different dental clinics and prefers treating patients with a multi-disciplinary approach with a team of highly skilled colleagues in different dental specializations. Her professional credo unequivocally is "Save The Teeth You Were Born With!". One of her passions is treating patients by a perio-ortho approach in collaboration with a master of orthodontics for periodontal patients - dr. Eglė Zasčiurinskienė.
To fulfill her mission to educate, Laura can often be found presenting lectures at dental events at a national level. She also started her own business OS SANUM (www.issiziok.lt) with a goal to educate and provide high-quality oral care hygiene products to her colleagues as well as patients.
In her spare time, she likes to hike and bicycle in nature, read, travel, cook and share meals with her friends and family, learn ballet, and paint using intuitive art techniques. Each of the paintings on her walls at home tells you a story you would have not known otherwise. Yet her favorite thing of all is to share quality time with her loved ones.

PhD portfolio

PhD candidate:	**Laura Žiūkaitė**
Graduate school:	Dentistry
Position:	Buitenpromovendus
PhD period:	2015-2023
Official admission:	08-11-2016
ORCID:	0000-0002-3589-9752

Promotors:

prof. dr. G. A. van der Weijden	Department of Periodontology
prof. dr. D. E. Slot	Department of Periodontology

PhD training

School of Dentistry ACTA

	Year	ECTS
Guidance and training *(Tutoring, mentoring, supervising)*	Continuously	8
Course writing and presenting in English *(incl.preparation for TOEFL exam)*	2011	4
Course on scientific integrity	2022	2
		Subtotal: 10

Specialist training in Periodontology and Implantology, Department of Periodontology ACTA
Tandarts Parodontoloog in Opleiding (TPO)

	Year	ECTS
	2011-2014	180

This included education on:
Functional anatomy of the head and neck
Biology of the periodontium and oral physiology
Microbiology of dental plaque
Clinical features and diagnosis of periodontal diseases
Therapy of periodontal disease – non-surgical therapy
Therapy of periodontal diseases – periodontal surgery
Wound healing of periodontal surgery
Treatment of furcation problems
Critical evaluation of the literature

Pathogenesis of inflammatory periodontal diseases
Epidemiology of periodontal disease
Manifestations of systemic disorders in the oral cavity
The medically compromised patient
Antimicrobial treatment of periodontal disease
Occlusal trauma
Radiological diagnosis
Pharmacology
Interrelationships of periodontal disease and therapy with other dental disciplines
Maintenance
Training in motivational interviewing.
Behavioural sciences
Course Statistics and Methodology
Clinical patient treatment
Case presentations and discussions

Subtotal: 190

Attended courses

Soft tissue management around natural teeth and implants. Hands-on training. M.Hurzeler. Amsterdam, The Netherlands	2013	0,64
Cone beam CT. Expertise requirements for the radiation protection professional. Afdeling Radiologie. ACTA.	2013	1,22
"Periodontal views across the border". Show your teeth. Afdeling parodontologie. ACTA.	2016	0,2
Paro-verwijzersavond. Afdeling parodontologie. ACTA	2016	0,13
"Botaugmentaties met de nieuwe generatie niet-resorbeerbare PTFE-membranen – Cytoplast" Memodent.	2016	0,14
Kadaverscursus hands-on; pre-implantologische chirurgie. ITI certificaat. Rotterdam, The Netherlands	2016	0,36
"Oral piercings, the beauty and the harm". Show your teeth. Afdeling parodontologie. ACTA	2017	0,12
Reconstructive periodontal plastic surgery in the aesthetic zone. G. Zucchelli. Bologna, Italy	2018	0,72

Opfriscursus stralingshygiëne voor tandartsen en orthodontisten. ACTA.	2018	0,18
Visitatietraining Parodontologen NVvP. Arnhem, The Netherlands.	2018	0,31
NVvP thema-avond "De nieuwe classificatie". Vinkeveen	2019	0,11
NVvP webinar "Parodontitis en multi-causaliteit: een kijkje achter het scherm van de wetenschap".	2020	0,12
NVvP webinar "Antibioticagebruik in parodontologie"	2020	0,12
Reconstruction of periodontal and peri-implant tissues: fundamentals of microsurgery. Theory and hands-on training. Serhat Aslan. Vilnius, Lithuania.	2022	0,64
Current actualities in Periodontology. Vilnius, Lithuania.	2022	0,18
		Subtotal: 5,19

Attended international conferences

EuroPerio 7. Viena, Austria.	2011	0,75
International Jan Lindhe symposium. Gotthenburg, Sweden.	2014	0,36
100th Annual meeting of American Academy Periodontology. San Francisco, USA.	2014	1,14
EuroPerio 8. London, United Kingdom.	2015	0,75
ITI Congress Norway & Sweden. Oslo, Norway	2019	0,36
EuroPerio 9. Amsterdam, The Netherlands	2018	0,75
EuroPerio 10, Copenhagen, Denmark	2022	0,75
		Subtotal: 4,86

Attended international conferences

NVvP Najaarscongres.	2011	0,18
NVvP Najaarscongres.	2012	0,18
NVvP Voorjaarscongres.	2013	0,18
NVvP Najaarscongres.	2013	0,18
Lustrumcongres 25 jaar Paro Praktijk Utrecht & Praktijk voor Parodontologie en Implantologie Nijmegen. Ermelo, The Netherlands	2014	0,25

NVvP Voorjaarscongres.	2014	0,18
Health investment. "Uitdagingen in de diabetes zorg". Symposium Diabetes Academie. Veenendaal, The Netherlands	2018	0,2
VMTI congres "O wee o wee, Zwangerschap voor zorgprofessionals" . Soest, The Netherlands	2018	0,2
NVvP Najaarscongres "Dentech". Ede, The Netherlands.	2018	0,18
ITI Congress Benelux Rotterdam. Rotterdam, The Netherlands	2019	0,36
		Subtotal: 2,09

Given lectures and presentation

E-poster presentation "The prevalence of diabetes among referred periodontal population". EuroPerio 8, London, United Kingdom.	2015	0,5
Poster presentation "Direct access to a dental hygienist: characteristics of the patient population". IADR, San Francisco, United States.	2016	0,5
Oral Presentation "When periodontal patient becomes one of implantology. The pathway to predictability" Lithuanian Prosthetic Congress "LOOD" Vilnius, Lithuania	2017	0,5
E-poster presentation "Do diabetics lose more teeth?" EuroPerio9, Amsterdam, The Netherlands	2018	0,5
Oral Presenation "Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: a systematic review and meta-analysis of epidemiological studies" VMTI Onderzoeksprijs	2018	0,5
Oral presentation ""Discussion and management of clinical situations in dentistry: what's left behind the scenes". Kaunas region annual winter congress Kaunas, Lithuania	2022	0,5
		Subtotal: 3
		Total: 205,14

Reviewer for international scientific journal
International Journal of Dental Hygiene.

Co-author of other publication:
An integrative approach for comparing microcirculation between normal and alveolar cleft gingiva in children scheduled for secondary bone grafting procedures. Milstein, Dan M. J.; Cheung, Yuk Wah; Ziukaite, Laura; Ince, Can; van den Akker, Hans P.; Lindeboom, Jerome A. H. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Mar;115(3):304-9.

Awards:
First place for **Publication of the year** (Prevalence of diabetes mellitus among periodontal patients. A systematic review and meta-analysis) awarded by Dutch Society of Periodontolgy (NVvP) (2018).

First place for the **Research Prize** awarded by Association of Medical Dental Interaction (VMTI) (2018).

WILEY **Top Cited Article** 2021-2022 International Journal of Dental Hygiene "The risk of tooth-loss in patients with diabetes: a systematic review and meta-analysis" (2023).

Memberships:
Dutch Society of Periodontology (Nederlandse Vereiniging van Parodontologie NVvP)

EFP Alumni community

Lithuanian Society of Periodontology

Identifiers
Web of Knowledge

Papers found	5
Times Cited	61
Times Cited (without self-citations):	58
Average citations per item	12.2
H-index	4
Average citations per year	15.6

Academisch Centrum Tandheelkunde Amsterdam (ACTA)

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Step by step.

Aušra

PERIODONTOLOGY

AČIŪ