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Bidirectional association between periodontal disease and diabetes mellitus: A systematic review and meta-analysis of cohort studies

Dissertation

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Zusammenfassung:
Diabetes mellitus und Parodontitis sind beides chronische Erkrankungen, die weltweit eine große Anzahl von Menschen betreffen und somit ein bedeutendes globales Gesundheitsproblem darstellen. Die vorhandene Literatur deutet bereits darauf hin, dass es einen Zusammenhang zwischen den beiden Erkrankungen gibt, und in den letzten Jahren wurde viel Forschungsarbeit zu diesem Thema geleistet. Studien zeigen, dass die Prävalenz von Parodontitis bei Personen, die bereits an Diabetes mellitus erkrankt sind, signifikant höher ist als bei Gesunden. Umgekehrt wurde gezeigt, dass der Schweregrad der Parodontitis einen Einfluss auf die glykämische Kontrolle bei Menschen mit Diabetes und weitere diabetesbedingten Komplikationen hat. Ziel dieser Arbeit ist es daher, die bestehende Evidenz zum bidirektionalen Zusammenhang zwischen Parodontitis und Diabetes mellitus systematisch in einer Metanalyse zusammenzufassen und zu bewerten. Um klare Aussagen über die Richtung der Assoziation zwischen den beiden Erkrankungen treffen zu können, werden prospektive und retrospektive Kohortenstudien einbezogen, die einen klaren zeitlichen Verlauf darstellen. Darüber hinaus wurde das Verzerrungsrisiko der einzelnen Studien untersucht, wobei der Schwerpunkt auf der Diagnosemethode der beiden Erkrankungen lag, da hier eine große Variabilität besteht. Unsere Ergebnisse der Metaanalyse zeigen, dass Menschen mit Diabetes ein 24% (95% Konfidenzintervall: 13%; 37%, n=7 Studien) höheres relatives Risiko haben, an Parodontitis zu erkranken und umgekehrt ist das Risiko, an Diabetes zu erkranken, bei Menschen mit Parodontitis um 26% (95% Konfidenzintervall: 12%; 41%; n= 10) erhöht. In den einzelnen Studien wurden die Diagnosen entweder durch Selbstauskunft, verschiedene klinische Untersuchungen oder eine Kombination aus beidem gestellt. Trotz der großen Heterogenität zeigten sich in den Subgruppenanalysen hierzu keine wesentlichen Unterschiede, jedoch ist die Anzahl der Studien zu gering, um hier eine schlüssige Aussage zu machen. Somit sollten in künftigen Studien klare und einheitliche Diagnosekriterien und Schwellenwerte verwendet werden, um eine Vergleichbarkeit gewährleisten zu können. Die Ergebnisse zeigen, wie wichtig eine interdisziplinäre Zusammenarbeit zwischen Zahnmedizin und Allgemeinmedizin ist, um Patienten, die entweder an Parodontitis oder an Diabetes leiden, darauf aufmerksam zu machen, dass diese beiden Erkrankungen miteinander in Verbindung stehen und die eine Krankheit die andere verschlechtern kann, wenn sie unbehandelt bleibt. Dadurch lassen sich frühzeitig präventive Maßnahmen ergreifen und somit die Auswirkung auf die allgemeine Gesundheit verbessern.

Summary:

Diabetes mellitus and periodontitis are both chronic diseases affecting a large number of people worldwide and thus represent a major global health problem. The existing literature already indicates that there is an association between the two diseases and much research has been done on this topic in the recent years. Studies demonstrated that the prevalence of periodontitis is significantly higher in individuals with diabetes mellitus than in healthy individuals and conversely, the severity of periodontitis has been shown to have an impact on glycemic control in people with diabetes and further diabetes-related complications. Therefore, the aim of this work is to conduct a systematic review and meta-analysis on the bidirectional association between periodontitis and diabetes mellitus in order to summarize and evaluate the existing evidence on this topic. In order to make clear conclusions about the direction of the association between the two diseases, prospective and retrospective cohort studies that present a clear time course are included. In addition, the risk of bias of each study was assessed, with a focus on the method of diagnosis of the two diseases, as there is a high variability here. The findings of our meta-analysis show that people with diabetes have a 24% (95% Confidence interval: 13%; 37%, n= 7 studies) higher relative risk of developing periodontal disease and vice versa, the incidence of diabetes is elevated by 26% (95% Confidence interval: 12%; 41%, n= 10) for people with periodontitis. In the individual studies, the diagnoses were assessed either by self-reports, different clinical examinations or a combination of both. Despite the great heterogeneity, no differences were shown in the subgroup analyses on the diagnostic methods, but the number of primary studies is too small to draw conclusive statements. Thus, clear and consistent diagnostic criteria and thresholds should be used in future studies to ensure comparability. In conclusion, the results show the importance of interdisciplinary cooperation between dentistry and general medicine to make patients with either periodontitis or diabetes aware that these two diseases are associated with each other and that one disease can worsen the other, if left untreated. This will allow preventive measures to be taken at an early stage and thus improve the impact on public health.

List of abbreviations:

Advanced glycation endproduct	AGE
American Academy of Periodontology	AAP
American Diabetes Association	ADA
Centers for Disease Control and Prevention	CDC
Clinical attachment loss	CAL
Community Periodontal Index	CPI
Hemoglobin A1c	HbA1c
Interleukin-1ß	IL-1ß
Osteoprotegerin	OPG
Polymorphonuclear leucocyt	PMN
Probing pocket depth	PPD
Prostaglandin E2	PGE2
Receptor activator of nuclear factor kappa B ligand	RANKL
Receptor of advanced glycation endproducts	RAGE
Recession	REC
Russell's Periodontal Index	PI
Tumornecrosis factor-alpha	TNF-alpha
US-Dollar	USD
World Health Organization	WHO

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1 General Introduction

1.1 Backround

Diabetes mellitus and periodontal disease are both widespread chronic diseases that represent a major global health problem.[1] The number of adults (20-79 years) suffering from diabetes mellitus is estimated at 59 million in Europe and at 463 million worldwide in 2019. Despite the high number, it is still assumed that more than 50% of those affected are undiagnosed and it is estimated that by 2045 about 700 million adults will be affected by the disease.[2] Also the extent of chronic periodontal disease should not be underestimated as it is generally assumed that 90% of adults worldwide suffer from periodontal disease, if reversible gingivitis is included. If only the destructive form, periodontitis, is considered, about 50% of adults globally are affected.[3] In 2010, the severe form of periodontitis was the sixth most common disease worldwide with 743 million people affected.[4] In addition, a study showed that over 70% of adults aged 35 to 44 years in Germany had deepened periodontal pockets.[5] In the recent years, much research has been done on the bidirectional association between the two diseases. There are studies that show that periodontal disease is more prevalent in people with diabetes than in healthy people and severe periodontitis is more common in individuals who have poorly controlled diabetes with elevated Hemoglobin A1c (HbA1c) values.[6] On the other hand, it has been shown that the severity of periodontal disease has an influence on the regulation of blood sugar levels in individuals suffering from diabetes as well as on the development of diabetes-related complications.[7].

1.2 Diabetes mellitus

1.2.1 Pathomechanism/ definition

Diabetes mellitus is a group of chronic metabolic disorders that are characterized by abnormal glucose metabolism leading to elevated blood glucose levels, known as hyperglycemia.[2] The cause of this condition is either a defect in the production of the hormone insulin, which is necessary to transport glucose from the blood stream into the body cells or a resistance of the body cells to insulin, or both.[2]

The American Diabetes Association (ADA) has categorized diabetes into four main groups: Type 1 diabetes, type 2 diabetes, gestational diabetes and specific types of diabetes due to other causes.[8] As we have only examined studies with type 1 or 2 diabetes in our meta-analysis, the focus is on these two forms. Type 1 diabetes is characterized by an autoimmune destruction of the ß-cells of the pancreas, which leads to very little or no secretion of insulin. Only 5-10% of diabetics suffer from this form, the onset of the disease is usually in childhood or adolescence but it can affect any age group.[9] This autoimmune process is based on a combination of many genetic predispositions and environmental factors that are still not fully understood. With 90% of cases, type 2 diabetes is the most common form of diabetes, which occurs mainly in older adults, but also increasingly in younger people.[2] In type 2 diabetes, the body cells are resistant to insulin and thus the patients suffer from a relative insulin deficiency, which is initially compensated by an increased insulin production of the pancreatic ß-cells. Over time, however, this hyperinsulinemia is no longer sufficient to cover the insulin requirement and this elevated secretion causes dysfunction and failure of the ß-cells, which finally leads to hyperglycemia.[10] The disease is often not diagnosed for years because the hyperglycemia develops slowly and typical symptoms (for example: polydipsia, polyuria and weight loss) as in type 1 diabetes do often not appear.[11]

1.2.2 Diagnosis criteria

The diagnostic criteria for diabetes according to the ADA is either a plasma glucose criterion or a A1C criterion: Fasting plasma glucose $\geq$ 126 mg/dl or 2-h plasma glucose $\geq$ 200 mg/dl after a 75 g oral glucose tolerance test or an HbA1c value $\geq$ 6,5% or having typical symptoms of hyperglycemia and a random plasma glucose $\geq$ 200 mg/dl.[11] This different diagnostic test are considered to be equally adequate but it has been found that the 2-h plasma glucose test diagnoses more patients with diabetes.[11]

1.2.3 Risk factors and complications

Even though the causes of diabetes mellitus have not yet been researched in detail, a combination of several genetic predispositions and environmental factors is assumed. Risk factors contributing to the onset of type 2 diabetes include especially increasing age, family history of diabetes and overweight and obesity.[2] In this context, it has been shown that the risk of diabetes can be reduced mainly by lifestyle changes that lead to weight loss. Thus, physical activity and a healthy diet are important modifiable factors inversely related to the incidence of type 2 diabetes.[12,13] In addition, lower levels of education and income as well as smoking are associated with a higher risk of developing type 2 diabetes.[14,15] Diabetes is associated with many possible long-term macro- and microvascular complications, as chronically elevated blood glucose levels can lead to glycosylation of proteins and lipids in blood and tissue. These include in particular cardiovascular diseases, as people with diabetes have been shown to have approximately a two-fold increased risk of coronary heart disease[16]. Further diabetes-associated diseases are diabetic retinopathy, that is one of the leading causes of blindness[17], chronic kidney disease[18] and diabetic neuropathy.[19] There are also co-morbidities that are related to diabetes, such as cancer.[20] In addition, it is estimated that 4.2 million adults died of diabetes mellitus and its complications in 2019, accounting for 11.3% of all deaths globally.[2] Finally, in recent decades more and more research has been conducted on the impact of diabetes on oral health. It has been shown that the prevalence of hyposalivation, oral lesions such as candidiasis and oral mucosal ulcers, gingivitis and periodontitis is increased in people suffering from diabetes, especially when uncontrolled diabetes is present.[21] Special attention should be paid to the increased risk of periodontitis in patients with diabetes, as the prevalence and the severity of the disease are shown to be higher than in healthy individuals, which acknowledges the symptoms of periodontitis as a complication of diabetes. [22] The risk of periodontal disease and associated future tooth loss increases disproportionately with increasing levels of glycated hemoglobin.[23]

1.2.4 Global burden

In addition to the health consequences, diabetes also has a major economic impact as the direct costs of diabetes have increased in recent years. While healthcare expenditure due to diabetes was US-Dollar (USD) 232 billion in 2007, it is expected to rise to USD 760 billion worldwide in 2019 with serious implications for global health budgets.[2] Account must also be taken of the indirect costs, which are mainly caused by loss of manpower and mortality and amounted to 454,81 billion USD in 2015.[24] In Germany, the direct and indirect costs for people with diabetes are two and three times higher than for people without diabetes.[25] The Costs of DiabetesMellitus study, which uses the database of the statutory health insurance in Germany from 2001, shows that in Germany the direct costs of patients with diabetes account for 30.6 billion euros which corresponds to 14.2% of the total health expenditure.[26]

1.3 Periodontal disease

1.3.1 Pathomechanism/ definition

Periodontal disease is a multifactorial inflammatory disease, which has its origin in a biofilm of mainly anaerobic gram-negative bacteria on the tooth surface.[27] The accumulation of bacteria in the early stages initially leads to inflammation of the gums, the so-called gingivitis. It is a reversible stage, clinically characterized by redness, swelling and bleeding of the gingiva.[28] By proliferation and spread of the dental plaque along the tooth root it can lead to periodontitis, an infection and progressive destruction of the tooth supporting structures, namely the collagen attachment fibres and the alveolar bone. This destruction can be explained by bacterial products, such as lipopolysaccharide, which trigger an inflammation cascade and interfere with the host defence through interaction with mononuclear phagocytic cells.[29] This induces the production of cytokines, such as Interleukin 1ß (IL-1ß) and Tumor necrosis factor alpha (TNF-alpha), and the expression of enzymes like matrix metalloproteinase. A chain of inflammatory events ultimately leads to progressive connective tissue degradation and resorption of the alveolar bone.[30] Clinically, the disease leads to the formation of deepened periodontal pockets, attachment loss, bleeding on probing, and can subsequently lead to

tooth loosening or even loss.[31] Figure 1 shows the effect of progression of periodontal disease on the tooth-sustaining apparatus.

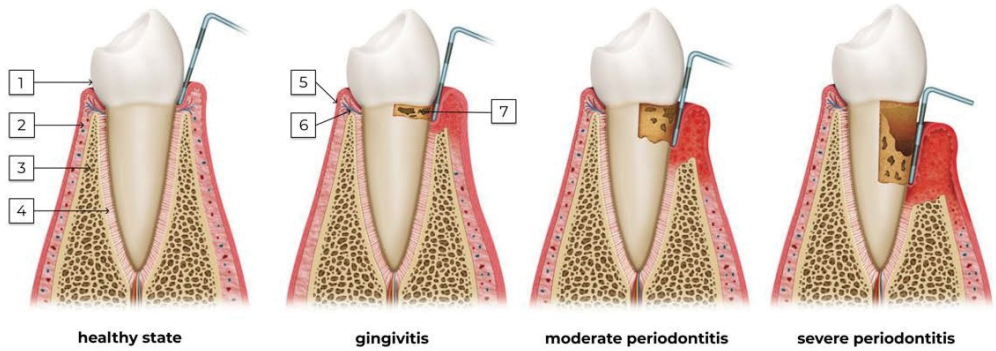

Fig. 1: **progression of periodontal disease:** 1) Tooth enamel 2) Gingiva 3) Alveolar bone 4) Periodontal ligament 5) Oral epithelium 6) Sulcus epithelium 7) Biofilm. Modified by Glurich et al.[32]

In a healthy state, the tooth is connected to the alveolar bone by the periodontal ligament, which consists of collagen fibres that are well innovated and vascularised. The crestal part of the jawbone and the cervical root surface are connected by tight collagen fibres, the gingiva. This is also connected to the cervical enamel via a connecting epithelium, which is connected to the sulcus epithelium lining the gingival sulcus and the oral gingival epithelium. Even in a healthy state, the tooth surface in the area of the gingival sulcus is colonised with bacteria, which are predominantly gram-positive. In this condition, an intact epithelial barrier prevents the bacteria from penetrating the underlying connective tissue and while some bacterial products can diffuse through the epithelium, the host defence with the polymorphonuclear leucocytes (PMNs) limits the harmful penetration of these products. If environmental factors shift the balance between host and parasite in favour of the bacteria, the composition and quantity of the resident microflora can change.[33] In response, there is initially increased immigration of PMNs into the epithelium and dilatation of the vascular plexus beneath the epithelium, leading to destruction of the collagenous fibres of the gingiva. Clinically, this leads to swelling and redness of the gingiva and can be referred to as a condition of gingivitis. Through these mechanisms, the body can

establish a new equilibrium between host and bacteria and the condition can remain stable for a longer period of time.[34] The progression of inflammation can occur due to the shift of subgingival bacteria from gram-positive to predominantly gram-negative species and a number of other environmental and acquired risk factors, such as cigarette smoking and genetics, that influence the immune response.[35] It has been shown that the presence and number of certain periodontal bacteria is significantly associated with the presence of deep periodontal pockets, these bacteria include those of the so-called red complex: Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola.[36] In particular, Prorpgyromonas gingivalis is thought to have specific mechanisms to interfere with the host immune system and thus disrupt the homeostasis between host and bacteria, leading to destructive changes in the periodontium.[37] As inflammation progresses, plasma cells are found in the connective tissue as the predominant cells of the inflammatory infiltrate, there is epithelial proliferation into the infiltrated connective tissue and increased drainage of cells and fluid from the sulcus. These destructive processes lead to the stage of periodontitis, which is accompanied by bone resorption, pocket formation and apical migration of the junctional epithelium.[34] In summary, every periodontitis initially requires gingivitis, but conversely not every gingivitis must progress to periodontitis.[38] In order to establish periodontitis, certain periodontal pathogens and a susceptible host whose immune system cannot prevent bacterial invasion must be present.[39]

1.3.2 Classification / diagnosis criteria

Since 1999 there has been a unified classification system, by the American Academy of Periodontology (AAP), of periodontal disease into different subgroups: Gingival diseases, chronic periodontitis (characterized by slow progression), aggressive periodontitis (characterized by a rapidly progressing destruction and occurs mainly in younger people), periodontitis as a manifestation of systemic disease (can be associated with hematological diseases as leukemias or genetic diseases as down syndrome), necrotizing periodontitis (characterized by necrotic lesions of the soft tissue), periodontal abscess, periodontitis associated with endodontic lesions and developmental or

acquired conditions.[40] Here we focus on the most common form of periodontal disease in adults, chronic periodontitis. Based on this classification system, it can be further subdivided according to severity and extent. The severity is based on the measurement of the clinical attachment loss (CAL): CAL of 1-2 mm corresponds to a mild periodontitis, CAL of 3-4 mm to a moderate periodontitis and CAL ≥ 5 mm to a severe periodontitis.[40] The extent is based on whether ≤30% or >30% of the sites correspond to a respective value and is thus classified as localized or generalized periodontitis.[41] In 2018, a new classification system was developed by the AAP and European Federation of Periodontology,[42,43] as the previous system had persistent diagnostic imprecisions and implementation problems, including the differentiation of aggressive and chronic periodontitis. Therefore the two forms have been combined to periodontitis, as different etiology and pathogenesis are insufficiently detectable.[42] Periodontitis is further specified by a staging and grading system, while staging describes the severity of the disease in the current situation, grading indicates the risk of progression. The stage is classified on the basis of the interproximal CAL or, if not present, on the radiographic bone loss. If information about tooth loss due to periodontitis is available, the stage can be modified. Additionally, complexity factors such as probing pocket depth (PPD) or tooth mobility may lead to classification in a higher stage. The primary criterion for the grade classification is radiographic bone loss or CAL over the last 5 years. Risk factors such as smoking and diabetes can modify the grade: If there is an additional diagnosis of diabetes this can cause a shift from grade A to grade B, if the HbA1c value is <7%, a grade C corresponds to a HbA1c value ≥7%.[42,43] The most commonly used clinical parameters that are assessed are therefore CAL and PPD: PPD is the distance between the gingival margin and the base of a periodontal pocket, while CAL is the distance between the cementoenamel junction and the lowest point of the periodontal pocket.[44,45] Therefore, the Centers for Disease Control and Prevention (CDC) and the AAP have recommended a clinical case definition for studies of periodontitis, based on a combination of PPD and CAL measurements.[44] Furthermore, the World Health Organization (WHO) has introduced the Community Periodontal Index (CPI), which examines all teeth for the presence of gingival bleeding and PPD,

to provide a consistent method to obtain an estimate of periodontal attachment destruction.[46] Thus, the index is well applicable in larger epidemiological studies and can be structured into the following scores: score 0= periodontal healthy; score 1= gingival bleeding; score 2=gingival bleeding and dental calculus; score 3=4-5 mm PPD; score 4=≥6 mm PPD.[47] Another index is Russell's Periodontal Index (PI), a purely visual classification of the inflammation without measurements of clinical parameters.[48] A systematic review has shown that only a small number of relevant publications (15 out of 104) used quantitative case definitions and that even these have a heterogeneity in the methods and thresholds used to diagnose periodontitis, which may pose the problem of over- or underestimating the prevalence of the disease.[49]

1.3.3 Risk factors and complications

There is a large heterogeneity in the prevalence of periodontal disease with respect to sociological-ecological conditions and behavioral risk factors. It was shown that people with a lower socioeconomic status had a 10-20% higher prevalence and severity of periodontal disease than people with a higher status. This can be explained, among other things, by the fact that oral hygiene behavior varies according to educational level and income. It is also possible to show a different distribution of the disease between rural areas and cities.[50] Within the same area, there are also differences according to race, and within the same age group, African Americans are twice as likely to have periodontitis as Caucasian Americans.[51] Studies have also demonstrated that severity and prevalence are higher in older age groups than in young people.[52,53] However, it is still unclear whether this is only due to the fact that the extent of periodontitis is greater due to the cumulative effect of destruction over a longer period of time.[54] An association between the male sex and the more frequent occurrence of periodontitis can also be shown if it is taken into account that men have poorer oral hygiene and visit the dentist less frequently.[53] Further, some behaviors are considered an important risk factor for periodontal disease. These include cigarette smoking, as smokers show a two to seven times higher risk of attachment loss compared to non-smokers,[55] and there is a dose-response

relationship between smoking and the severity of periodontal disease.[56] According to recent research, genetics is also an important factor in the development and severity of periodontal disease. This significance of genotype has been demonstrated by twin studies, which showed that genetic differences are a determinant of risk in periodontitis.[57] Genetic variations that alter the host defence response have been demonstrated. For example, a genotype of the polymorphic IL-1 gene cluster associated with high IL-1 production was identified. As IL-1 is an important modulator of host response, extracellular matrix catabolism and bone resorption, it has been shown to be a strong indicator of susceptibility to severe forms of periodontitis.[58] In addition, various systematic diseases have been associated with an increased risk of periodontitis, and for diabetes mellitus in particular, there is ample evidence of a higher prevalence and a more severe form of the disease.[59] A meta-analysis from 2018 reports an 86% higher risk for the incidence and progression of periodontal disease in not well controlled individuals with diabetes than in individuals without diabetes or well controlled diabetes.[60] Also the systemic disease osteoporosis, characterized by lower bone density, can lead to a decrease in alveolar bone in conjunction with periodontal infection.[59]

1.3.4 Global burden

In addition to health aspects, the impact on the global economy should also be considered, as the WHO estimates that oral diseases are the fourth most costly disease to treat. In 2010, the direct treatment costs of dental diseases worldwide amounted to approximately USD 298 billion and the indirect costs to about USD 144 billion, of which 38% were caused by severe periodontitis alone.[61]

1.4 Current evidence on diabetes mellitus and periodontal disease

There is much evidence in the literature for an association between periodontal inflammation, glycemic status and diabetic-associated complications. First, it has been shown that periodontal disease, due to the existing chronic inflammatory burden, makes control of diabetes difficult and increases associated

complications. On the other hand, the condition of hyperglycemia also has negative consequences for the periodontal situation.[3] There is a meta-analysis from 2017 that examined the current evidence for the association between periodontitis and diabetes, with the result that the prevalence of diabetes mellitus is higher in patients with existing periodontitis.[62] However, only cross-sectional studies were included and therefore no temporal course is evident. It is necessary to conduct a meta-analysis on this topic, which includes only prospective cohort studies, in order to clarify which disease was present at the beginning and thus to show the direction of the association between diabetes mellitus and periodontitis. The results further show that the prevalence for diabetes is higher when clinically diagnosed than when self-reported.[62] This shows that when interpreting the original studies, special attention must be paid to their risk of bias and the method used to establish the diagnosis plays an important role. Another meta-analysis examined the other direction of the association, with the result that adults with diabetes have a higher prevalence and progression of periodontitis.[60] Again, not only prospective studies are included and no clear exposure and outcome was defined. As exposure, prediabetes and diabetes were combined and no differentiation between the conditions was made. The outcome included not only the onset of periodontitis but also its progression. Another meta-analysis, which included predominantly cross-sectional studies, also found a higher prevalence of periodontal disease in type 2 diabetics than in healthy individuals. In addition to the lack of traceability of the chronological progression, a further weakness here is that only a few confounders were adjusted.[63] Moreover, in some studies tooth loss was equated with the presence of periodontal disease.[64-66] Tooth loss can be a relevant marker for periodontitis, but since other diseases or accidents can also lead to tooth loss,[67] it should be evaluated separately to avoid bias and not be equated with the presence of periodontal disease.

1.5 Aims of the research work

Due to the identified research deficits regarding the bidirectional association between diabetes mellitus and periodontal disease, the goal of this dissertation is to answer the key question of whether a bidirectional association exists.

Therefore, the existing literature was reviewed and summarized in a systematic review and meta-analysis. The aim was to include only prospective and retrospective cohort studies and not cross-sectional studies or case-control studies, so that a clear statement can be established as to which of the two diseases was present at the beginning and which has developed over the course of time with follow-up time. We want to present this time course of the association for both diseases separately and summarize it in a meta-analysis. Further, clear exposure and outcome points should be defined, so that a preexisting disease stage should not be considered in the same context as the disease itself, therefore prediabetes and gingivitis were excluded. Furthermore, only the occurrence of the disease should be considered as an outcome and not the progression of the disease. Since there are studies that have evaluated tooth loss as a marker for the presence of periodontitis, tooth loss was excluded as exposure/outcome to avoid bias. An important focus should be placed on evaluating the quality/risk of bias of the original studies, especially the method of assessment of the diagnosis periodontitis or diabetes. Finally, level of severity of periodontal disease regarding risk of incident diabetes was investigated in dose-response meta-analysis.

2 Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies,

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Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies

Julia Stöhr[1], Janett Barbaresko[1], Manuela Neuenschwander[1,2] & Sabrina Schlesinger[1,2]

Periodontal disease has been reported to be associated with diabetes mellitus. However, the direction of the association and the influence of bias are not clear. Thus, the aim of this systematic review and meta-analysis was to summarize the existing evidence on the bidirectional prospective association between periodontal disease and diabetes mellitus by accounting for the risk of bias of the original studies. The literature search was conducted on the electronic data sources PubMed and Web of Science up to February 9th, 2021. We included observational studies, which investigated the prospective association between diabetes mellitus and periodontal disease or vice versa. The risk of bias of the primary studies was evaluated by applying the Quality in Prognosis Studies (QUIPS) tool. Random effects models were used to calculate summary relative risk (SRR) with 95% CI. Subgroup analyses were applied to investigate heterogeneity and the robustness of the knding. In total, 15 studies were included . The SRR for incident diabetes mellitus was 1.26 (95% CI 1.12, 1.Ł1; I^2: 71%, n = 10; participants = Ł27,620; identiked cases = 11Ł,361), when comparing individuals with periodontitis to individuals without periodontitis. The SRR for incident periodontitis was 1.2Ł (95% CI 1.13, 1.37; I^2: 92%, n = 7; participants = 295,80Ł; identiked cases: > 22,500), comparing individuals with diabetes to individuals without diabetes. There were no signikcant differences between subgroups after stratikcation for risk of bias. The kndings show a positive bidirectional association between periodontal disease and diabetes mellitus, and thus, underline the need for screening of patients with periodontitis regarding diabetes mellitus and vice versa. The main limitation of the study is the high unexplained heterogeneity between the studies including the different assessment methods of the disease diagnosis.

Abbreviations

BMI	Body mass index
CAL	Clinical attachment loss
CPI	Community periodontal index
CI	Confidence interval
FPG	Fasting plasma glucose
HbA1c	Haemoglobin A1c
HR	Hazard ratio
ICD	International classification of disease
OR	Odds ratio
PI	Periodontal index
PPD	Periodontal pocket depths
PI	Predication interval
QUIPS	Quality in prognosis studies

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RR	Relative risk
SRR	Summary relative risk
WHO	World health organization

Diabetes mellitus is one of the most common chronic diseases worldwide and current estimates assume that 463 million adults were affected in 2019. The prevalence is projected to increase by almost 50% over the next years, and it is estimated that there will be about 700 million people living with diabetes by 2045[1]. Individuals with diabetes are at higher risk of developing further health-related complications and disorders, including cardiovascular disease[2], retinopathy[3], nephropathy[4] and neuropathy[5]. In addition, there is indication, that patients with diabetes suffer more often from dental disease (e.g. periodontitis) compared to individuals without diabetes[6]. Periodontitis is a widespread disease, whose most severe form afflicted about 743 million people worldwide in 2010, but an underestimation is expected[7]. The disease is characterized by a chronic inflammation of the entire periodontium that can irreparably destruct the tooth-surrounding tissue and result in the resorption of the alveolar bone. Consequences such as gingival bleeding, increased tooth mobility and tooth loss can be expected[8]. Recently, a meta-analysis summarized findings on glucose disturbance, including diabetes, and periodontal disease and indicated a positive association between these two factors[9]. However, in this meta-analysis, studies with different exposures and outcomes were mixed. For example, the authors combined studies on diabetes, prediabetes and diabetes severity[10,11]. In addition, the outcome was a mixture of periodontal disease and progression of the disease[12]. Moreover, there is indication that periodontal disease is a risk factor for diabetes mellitus[13]. Both conditions are driven by inflammatory processes, which might be a possible explanation for this bidirectional association[14]. To draw clear conclusions on these associations, a systematic review and meta-analysis is needed that considers methodological challenges when combining the existing data from primary studies. First, the time sequence of exposure and outcome needs to be taken into account to obtain the direction of the association. Second, the measurement of periodontal disease differs between the studies. In observational studies, periodontal disease has been assessed as self-reported periodontitis, clinical measurements attained from oral examinations (e.g. clinical attachment loss (CAL), periodontal pocket depth (PPD)), or established scores, such as the Community Periodontal Index (CPI; based on components including gingival bleeding, dental calculus and periodontal pocket depths), or Russell's Periodontal Index (PI; including signs of periodontal disease as inflammation, pocket formation and breakdown of function), respectively. Further, the risk of bias of the primary studies, including selection bias, information bias and confounding, should be considered by applying an appropriate tool[15] when interpreting the data.

Thus, our aim was to conduct a systematic review and meta-analyses of the existing evidence of observational studies, which investigate prospectively the bidirectional association between periodontal disease and diabetes mellitus. In addition, we accounted for the risk of bias of the original studies, especially the assessment of periodontal disease in our meta-analyses.

Research design and methods

The systematic literature search was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) guidelines[16]. A protocol has been registered in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=118829).

Search strategy. The literature search was conducted on PubMed and Web of Science up to February 9th, 2021 to identify studies analyzing the association either between diabetes mellitus and periodontal disease, or the other direction, respectively. We used a combination of predefined search terms developed for each database without applying filters or restriction of language and calendar date (Table S1). Furthermore, we checked the reference lists of identified related reviews and included articles if eligible. Four investigators (JS, JB, MN, SS) independently screened the titles and abstracts of the identified studies in EndnoteX8 and read the full-text, if the study seemed to be relevant. Disagreements were discussed and resolved by consensus.

Selection of studies. Studies were included, if: (1) they investigated the association between either periodontal disease and diabetes mellitus, or the other direction, respectively, (2) the association was investigated prospectively (this included prospective and retrospective cohort studies, nested case–control studies, case-cohort studies), (3) reported risk ratios (relative risk (RR), odds ratio (OR), hazard ratio (HR)) with corresponding 95% confidence intervals (CI) and 4) the papers were published following a peer-reviewed process.

Studies were excluded, if (1) they were animal studies, cross-sectional studies, case–control studies, conference abstracts or reviews, (2) they only reported crude estimates, (3) the study population was not relevant (including pregnant women or children and adolescents), (4) they focused on hyperglycemia (Fasting plasma glucose (FPG) > 110 ml/dg or haemoglobin A1c (HbA1c) > 6%) as exposure or outcome, (5) they focused on the progression of the particular disease and (6) when studies investigated potential indicators for periodontal diseases, such as tooth loss. In more detail, several studies investigated tooth loss as an indicator of periodontal disease,because assessing the number of missing teeth is less difficult and less time-consuming. However, tooth loss is not a reliable marker for periodontitis[17], as caries is another leading cause for tooth loss[18]. Thus, we decided to exclude tooth loss as exposure/outcome, to minimize bias.

If different studies reported on similar data (same exposure and outcome), we selected the study with the largest number of participants and cases.

Data extraction and risk of bias assessment. The extraction of the data from the studies was conducted by one investigator (JS or SS) and checked by two other investigators (JB or MN). Each inconsistency was

debated until agreement was reached. The following data were extracted from each eligible study: the last name of the first author, the name of the study and the country in which it was conducted, the study design (prospective and retrospective cohort studies), the publication year, follow-up time, number of participants and cases, definition and assessment of exposure and outcome, the exposure categories and number of cases and non-cases for each category, the RRs and 95% (CI) and the variables adjusted for in the analysis.

The risk of bias of the primary studies was evaluated by applying the Quality In Prognosis Studies (QUIPS) tool[15] by at least two independent investigators (JB, JS, MN) and discrepancies were discussed with another investigator (SS) and resolved by discussion. It includes the following 6 domains: study participation, study attrition, prognostic factor measurements, outcome measurements, study confounding and statistical analysis, and reporting. In each domain, the studies were evaluated for their reliability and eligibility and each domain was rated as low, moderate or high risk of bias. Finally, an overall risk of bias for each primary study was determined, whereby the domains prognostic factor and outcome measurements were assigned a higher weight, as we considered these domains to be of decisive importance. Thus, if a study was rated with high risk in one of these domains, the overall risk of bias was also judged as high. In this context, assessment of periodontal disease was judged as low risk of bias if clinical measurements of CAL or PPD were obtained, or ICD-codes based on the previously valid classification system for periodontal disease by Armitage (according to CAL) were used[19]. Further, we considered the CPI, introduced by the World Health Organization (WHO), as appropriate method, since it is faster and more reproducible in large epidemiological studies. The extend of PPD is the main factor for establishing the code and thus provides an indication for CAL[20]. A self-reported diagnosis that is validated by a dentist, classification by the PI and ICD-codes from a health insurance database, without further specification, were judged with moderate risk of bias. Self-reported diagnosis without validation is rated with high risk. The assessment of the diabetes mellitus diagnosis was classified with low risk of bias, if one of the following diagnostic tests was conducted, in accordance with the criteria of the American Diabetes Association: values of HbA1c or of plasma glucose (FPG or 2-h FPG after an oral glucose tolerance test)[21]. If a study included a self-reported diagnosis, validated by a physician or on ICD-codes from a health insurance database, it was considered to be at moderate risk. Diagnosis based on self-reports without validation were rated with high risk. For the domain study confounding, we defined the following confounders as important, for which a study should have at least been adjusted: age, sex, body mass index (BMI)/overweight, smoking status and socio-economic status. This domain could not be rated higher than moderate risk of bias, because residual confounding cannot be completely excluded in observational studies. In detail, the signaling questions for the QUIPS tool can be found in Table S2.

Statistical analysis. Meta-analyses were conducted for the following associations: (i) periodontal disease as exposure and incidence of diabetes mellitus as outcome, (ii) diabetes mellitus as exposure and incidence of periodontal disease as outcome. Summary relative risks (SRR) and 95% CIs for these associations were calculated by using random effects meta-analysis by DerSimonian and Laird[22]. In addition, we conducted dose–response meta-analyses for exposure on periodontitis, if it was measured as continuous variables (CPI or PPD), and studies provided findings (RRs and 95% CIs) for at least three quantified categories. For this, we calculated the study-specific slopes and corresponding 95% CIs from the natural logarithm of the reported RRs and 95% CIs across the exposure categories[23]. The shapes of the relationships were evaluated by using restricted cubic spline regression models, and a likelihood ratio test was used to test for non-linearity[24].

Heterogeneity was evaluated by applying I^2, tau^2, and 95% prediction intervals (95% PIs), and was investigated in subgroups analyses. Subgroup meta-analyses were conducted by total risk of bias, risk of bias for the exposure and outcome domains (high, moderate, low), sex, geographic locations, type of diabetes, duration of follow-up, number of cases, smoking status, and by adjustment of the original studies for potentials confounders: education, smoking status, overweight, fruit and vegetable intake, alcohol intake, physical activity, other chronic diseases. Differences were tested by using meta-regression[25]. Small study effects and publication bias were assessed by using Egger's test and by visual inspection of funnel plots[26], if more than 10 studies were included in the meta-analysis[27]. Potential publication bias was indicated by asymmetry of the funnel plot and a p value < 0.01 for Egger's test. All statistical analyses were conducted using Stata version 15.1 software (StataCorp, texas, US).

Certainty of evidence assessment. We evaluated the certainty of evidence for each association using the updated Grading of Recommendations Assessment, Development and Evaluations (GRADE). The GRADE tool covers the following aspects: the study design, the risk of bias of the primary studies, imprecision of the findings, inconsistency between the primary studies, indirectness in the primary studies, publication bias, the magnitude of effect of the pooled findings, indication for dose–response relations and the impact of residual confounding. The certainty of evidence can be evaluated as high, moderate, low or very low. A high certainty of evidence means that it is very likely that the effect estimate lies close to the true effect, whereas a very low certainty of evidence means that it is very likely that the inclusion of future studies will change the estimate.

Results

In total, 9384 studies were initially identified, and after removing 2427 duplicates and excluding 6411 articles by title and abstract, 546 were investigated in a full-text analysis (Figure S1). Finally, 15 cohort studies were included in our meta-analysis, the characteristics of all included studies are presented in the Supplemental Material (Table S4). A list of the excluded studies and the corresponding reasons are shown in the supplement (Table S3).

Periodontal disease and incidence of diabetes mellitus. We identified 10 studies that investigated the association between periodontal disease and incidence of diabetes mellitus with a total of 427,620 participants and 114,361 identified cases of diabetes mellitus over a mean follow-up period of 9.9 years (range

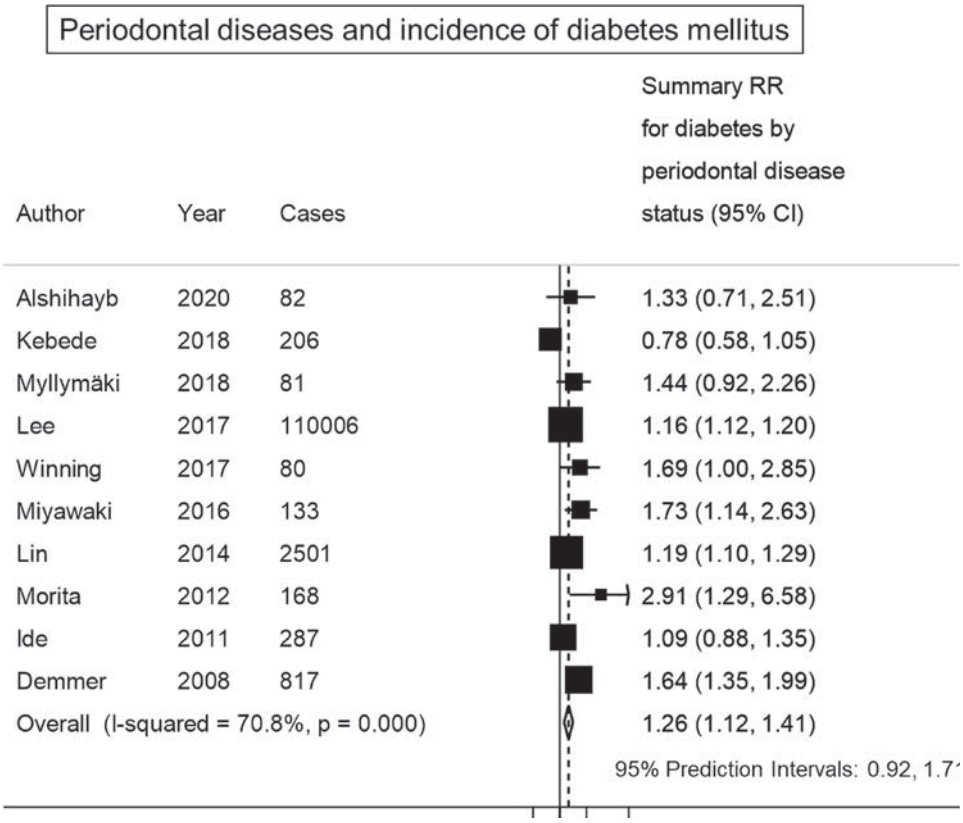

Figure 1. Meta-analysis of periodontal disease and incidence of diabetes mellitus.

5–17 years)[13,28–35]. Four studies achieved a low, three of them a moderate, and three a high overall risk of bias (Table S5). The assessment of periodontal disease was evaluated with low risk of bias in seven studies, moderate in one study, and high in two studies. The assessment of diabetes was judged as low risk of bias in seven, moderate in two studies, and high in one study. Eight studies focused on type 2 diabetes[13,28,31–35], one on both types[30], and for one it remains unclear which type of diabetes was investigated[29].

The SRR for incident diabetes mellitus was 1.26 (95% CI 1.12, 1.41; I^2:71%, Tau^2: 0.014, 95% PI: 0.92, 1.71), when comparing individuals with periodontitis to individuals without (Fig. 1). There was indication for a non-linear trend for the relationship between the CPI score and the incidence of diabetes. No association was observed for a CPI score ≤ 2, but an increase in the incidence of diabetes was observed after a CPI score ≥ 3 (score 3: SRR (95% CI): 1.38 (1.02, 1.87); score 4: SRR (95% CI): 2.33 (1.11, 4.87); p for non-linearity:0.090; n=2) (Fig. 2A). The non-linear analysis for the relationship between PPD and the incidence of diabetes showed an increased relative risk for diabetes up to a PPD of 3 mm, then the graph reached a plateau with no further increase in risk (PPD 1.0 mm: SRR (95% CI): 1.15 (0.83, 1.59); PPD 2.5 mm: SRR (95% CI): 1.27 (0.83, 1.95), PPD 3,5 mm: SRR (95% CI): 1.30 (0.90, 1.89), and PPD 4,5 mm: SRR (95% CI): 1.31 (0.86, 2.01), based on n= 2; p for non-linearity: 0.653) (Fig. 2B). The certainty of evidence was judged as moderate for the association between periodontal disease and incidence of diabetes mellitus (TableS6).

Diabetes mellitus and incidence of periodontal disease. The seven studies on diabetes mellitus and incidence of periodontitis included 295,804 participants and > 22,500 diagnosed cases of periodontal disease (missing information on cases for Lee et al. [36])[33,36–41]. The mean follow-up period was 11.1 years (range 5–20 years). The overall risk of bias was low in one study, moderate in four studies, and high in two studies (Table S5). Two studies were rated as low risk of bias regarding the exposure assessment, four as moderate and one study with high. Four studies focused on type 2 diabetes[37,38,40,41], one on type 1 diabetes[39], one on both types of diabetes[36], and in one it was not specified[33]. Outcome assessment was rated as low risk of bias in four studies, moderate for two studies, and high for one study.

The SRR for incident periodontitis was 1.24 (95% CI 1.13, 1.37; I^2: 92%, tau^2: 0.01, 95% PI 0.94, 1.65), comparing individuals with diabetes to individuals without diabetes (Fig. 3). The certainty of evidence was evaluated as moderate for the association between diabetes mellitus and incidence of periodontal disease (Table S6).

Subgroup analyses. There was no significant heterogeneity between subgroups after stratification by overall risk of bias, risk of bias in the exposure and outcome domains, sex, geographical location, type of diabetes, duration of follow-up, number of included cases, adjustment for important confounders (e.g. smoking status,

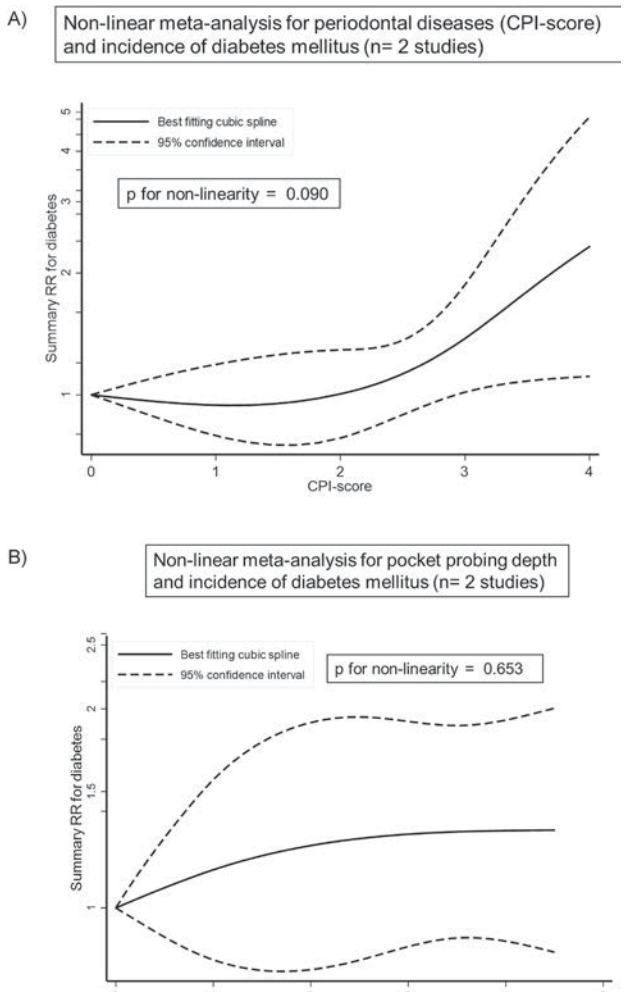

Figure 2. Non-linear dose–response meta-analysis for periodontal disease, defined as (**A**) CPI-score and (**B**) defined as PPD, and incidence of diabetes mellitus.

education, etc.) (Table S7–S8). Publication bias was only evaluated for the association between periodontal disease and incidence of diabetes mellitus because more than ten studies were available for these association, and no indication for publication bias was observed by visual inspection of the funnel plot (Figure S2) and Egger's test ($p=0.194$).

Discussion

This systematic review and meta-analysis of 15 cohort studies showed that there was a positive bidirectional association between both periodontal disease and diabetes mellitus with a moderate certainty of evidence. For patients with diabetes, the data indicated a 24% (95% CI 13%, 37%) increase in the incidence of periodontal disease. For patients with periodontitis, the relative risk of developing diabetes mellitus was elevated by 26% (95% CI 12%, 41%). These results coincide with those of the meta-analysis by Nascimento et al., where an 86% (95% CI 30%, 180%) increased relative risk of periodontitis for individuals with diabetes was found. The fact that the relative risk is higher than in our analysis may be due to the fact that different degrees of severity of diabetes were taken into account as exposure and the outcome was not only incidence of periodontitis but also progression of the disease and its marker[9]. In contrast, the meta-analysis by Ziukaite et al. focused on the other direction of the association and reported a 27% (95% CI 11%, 74%) higher prevalence of diabetes for patients with periodontitis[42], which is comparable to our findings. Risk of bias was high in the previous meta-analyses because different study designs, different definitions of exposure and outcomes were combined. In our meta-analysis, we considered both directions separately, included only prospective studies and did not mix disease status with pre-disease status or progression of the diseases, respectively.

In the risk of bias assessment of the individual studies, we particularly focused on the assessment and definition of periodontal disease and diabetes. In general, the diagnosis of a disease was defined by self- reports, clinical examinations or a combination of both. While a meta-analysis showed that the prevalence for diabetes was much

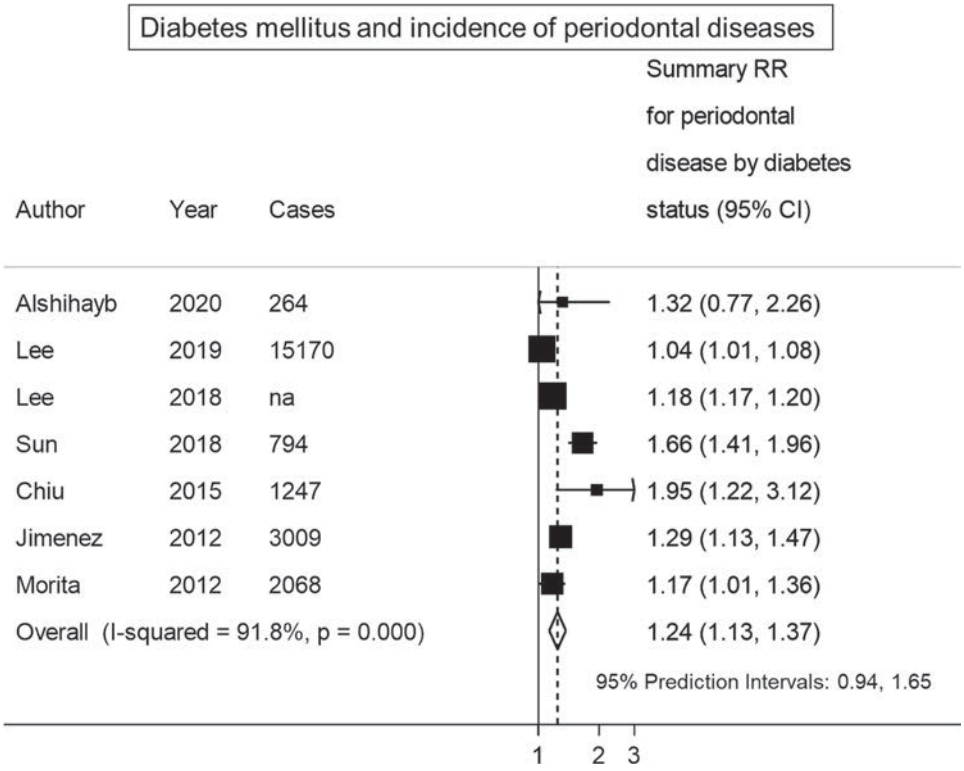

Figure 3. Meta-analysis of diabetes mellitus and incidence of periodontal disease.

lower for self-reported periodontitis compared to clinical periodontal measurements[42], our meta-analyses did not show a significant difference here. However, subgroup meta-analyses relied on small numbers of studies and more studies with accurate assessment methods are needed. Although it was rarely applied among the studies, assessment via CAL has been considered the gold standard for the classification of chronic periodontitis[19]. But with this method measurement errors may occur especially in the initial phase of periodontitis[43], for example, if the manual probe is applied with incorrect force, it can be advanced into intact attachment fibers[44]. It should also be taken into account that these measurements are associated with a standard deviation of 0.8–1.07 mm, even for experienced investigators[45]. Another applied assessment method is the determination of the PPD. While the assessment is more simple than the CAL, it has been shown that this method used alone, can lead to an underestimation of cases[46] because, especially with increasing age, the extent of PPD no longer correlates with CAL[47]. In addition, there are studies that used indices such as Russell's PI[28], or the CPI[13,33,37] to classify the disease. Periodontitis diagnosis based on the PI is critical because this index is only visually assessed and does not include clinical measurements, and it includes gingivitis as an early form of periodontitis[48]. Although the CPI is characterized by its reproducibility and simplification[49], it is not considered sufficient to describe the extent of periodontal disease[50]. In summary, the assessment and definition of periodontal disease vary widely across studies and there are no consistent thresholds for CAL/PPD and numbers of affected teeth to determine whether the disease is present or not. The Division of Oral Health at the Centers for Disease Control and Prevention in collaboration with the American Academy of Periodontology has provided a definition that combines measurements of CAL and PPD to assess periodontal disease to avoid misinterpretation of the periodontal status[48]. In order to make clear statements about the association between periodontitis and diabetes mellitus, it should be ensured in the future studies that established assessment of periodontitis is applied, and thus, enables comparability between studies.

There are many possible explanations for the observed bidirectional associations between periodontitis and diabetes, which are related to inflammatory processes. For example, on the one hand, untreated diabetes mellitus, both type 1 or 2 diabetes, lead to metabolic disorders caused by hyperglycemia[51]. Poor glycemic control in patients with diabetes has been shown to raise the level of systemic inflammation markers, e.g. interleukin-1ß, in the gingival crevicular fluid of a periodontal pocket[14], which is associated with the onset and severity of periodontal disease[52]. On the other hand, it has been show that gram-negative bacteria in the periodontal pockets elevate serum inflammatory markers such as c-reactive protein[53]. This can induce hyperinflammatory immune cells and promote the release of proinflammatory cytokines, which lead to insulin resistance[54].

Strengths of our meta-analysis is the bidirectional investigation and the dose–response meta-analysis between periodontal disease and diabetes mellitus by including only prospective studies and accounting for the major risk of bias sources, namely assessment of exposures and outcomes, and other sources of bias e.g. selection of participants and confounding. However, there are also limitations in our meta-analysis. First, as already described in detail, risk of bias regarding the assessment of periodontitis could not be ruled out in all of the studies. To account

for this, we conducted subgroup analysis and did not observe significant differences. However, these analyses were based on small numbers of studies, and should be treated with caution. Second, most of the included studies did not clearly differentiate between type 1 and type 2 diabetes. In the subgroup meta-analysis by type of diabetes, we did not observe substantial differences, but again, the number of studies in the subgroups were small. Third, residual confounding cannot be excluded because of the observational study design of the included studies. Fourth, the included studies did not report on repeated measurements and thus, we could not account for changes of the disease status (impairment or also improvement due to treatment). Fifth, we did not search for grey literature, because we prefer to include only peer-reviewed studies. Last, we identified high heterogeneity between studies, which may arise from different methodological aspects e.g. different assessment methods of periodontal disease and/or diabetes. However, we conducted several subgroups analyses and meta-regression for total risk of bias and risk of bias of exposure and outcome assessment, further factors such as geographic location, and methodological aspects (number of cases, duration of follow-up, adjustment for specific confounders etc.) and heterogeneity remained unchanged.

Our comprehensive meta-analysis can help investigators to plan and conduct further research regarding bidirectional associations between periodontal disease and diabetes mellitus and can help for decision making in the clinical context. Our findings support existing guidelines for physicians and dentists regarding the screening of patients with diabetes, which recommend that every new confirmed patient with diabetes mellitus, should be informed that there is an increased risk of developing periodontal disease and that glycemic control is more difficult in this case. Thus, every initial examination should include a periodontal evaluation[55]. It has been shown, that 40.7% of the dental patients without a diagnosis of diabetes (< 45 years) had HbA1c values around 5,7% or higher[56], thus, screening for diabetes mellitus in the dental office is as important.

In conclusion, there was a bidirectional association between periodontal disease and diabetes mellitus, even after stratifying for major risk of bias. However, only few studies with low risk of bias were available. To strengthen these findings more studies with valid assessment of periodontal diseases and diabetes are needed. The findings support current guidelines that patients with periodontitis should be screened for diabetes mellitus, and that patients with diabetes mellitus should be informed about their higher risk of developing periodontal diseases.

Data availability

All data are available in the manuscript and its Supplement file.

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of DistillerSR software for systematic reviews; Evidence Partners was not involved in the design or outcomes of the statement, and the views expressed solely represent those of the author.
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Author contributions

S.S. and J.S. designed the study question. J.S., J.B., M.N. and S.S. conducted the literature screening, and extracted the data. J.S., J.B., M.N. and S.S. assessed the risk of bias of the included studies. S.S. conducted the analyses and S.S. and J.S. interpreted the data and wrote the first draft of the manuscript. All authors critically reviewed the manuscript and approved submission of the final manuscript.

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Competing interests

The authors declare no competing interests.

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3 Discussion

3.1 Key findings

For our systematic review and meta-analysis, we identified seven studies on the association between diabetes mellitus and the development of periodontal disease. In addition, for the relationship between periodontal disease and incidence of diabetes, we identified 10 studies. For patients with diabetes mellitus the risk of developing periodontitis was 24% (95% CI: 13%, 37%) increased compared to patients without diabetes and on the other hand, people with periodontitis have a 26% (95% CI:12%, 41%) higher relative risk in the incidence of diabetes mellitus compared to persons without periodontitis. The findings are robust across stratified analyses, including subgroups such as type of diabetes, sex, duration of follow up, geographic locations and risk of bias in the exposure and outcome domains.[68]

3.2 Possible impacts of diabetes mellitus on periodontal disease

Since the results of our meta-analysis show that the relative risk of periodontitis is higher in people suffering from diabetes than in individuals without,[68] the biological mechanisms that can lead to periodontitis being influenced by diabetes mellitus should be discussed more closely. Both are chronic diseases associated with increased inflammation and decreased host immune response.[69] For the development of periodontal disease, two factors must be considered, the presence of specific periodontal pathogens and a weakened immune response of the body. Since it has been shown that the subgingival bacteria in periodontal pockets are not significantly different between individuals with diabetes and people without diabetes and similarly, the level of glycemic control showed no effect on the composition of subgingival plaque,[70] it can be assumed that diabetes leads to an increase in periodontal destruction by modifying the immune system.[71] Chronically elevated glucose levels in diabetics lead to irreversible glycosylation of proteins and lipids in blood and tissue. These so-called Advanced

Glycation Endproducts (AGEs) are the primary cause of diabetes-associated complications and have therefore also a negative impact on periodontal health. Hyperglycemia lead to the accumulation of AGE and a higher proportion of AGE in the periodontium.[72] The interaction of AGE with their receptors (RAGE), which are located on the surface of different cell types, trigger different reactions that lead to oxidative stress and alter host reaction mechanisms.[73] First, the interaction on monocytes/macrophages lead to the transformation of the cells into a hyperreactive phenotype,[73] which stimulate an excessive production of proinflammatory cytokines such as IL-1ß and TNF-alpha, in response to bacterial antigens such as those of porphyromonas gingivalis. Serum levels of these cytokines have been shown to be elevated in the sulcus fluid of periodontal pockets of diabetic patients compared to non-diabetic patients.[74] The cytokines are involved in the pathogenesis of periodontitis through an excessive inflammatory response and a decrease in the immune response. This process is related to the glycemic control, as the serum level in the crevicular fluid of patients with an HbA1c value > 8% is almost twice as high as in patients with a lower HbA1c value.[75] Furthermore, binding of AGE to RAGE on endothelial cells increases vascular permeability and interaction on fibroblasts decreases collagen production. Together, these interactions lead to a hyperinflammatory response with reduced wound healing and increased susceptibility to infection, which in gingival tissue is associated with tissue destruction and reduced repair, thus promoting progression of periodontal destruction. In addition to binding AGE to its receptors, it accumulates in the periodontium of diabetics and binds to collagen crosslinks, forming highly stable collagen macromolecules.[76] These accumulate in vessel walls and bind low density lipoproteins, which lead to atherosclerotic vascular changes.[77] AGE-modified collagen is also deposited in the basement membrane of endothelial cells, causing them to thicken. These gingival microangiopathies can impede oxygen diffusion and hemostatic transport, thus reducing the tissue's resistance to periodontal disease.[78] AGE collagen ultimately leads to disrupted connective tissue and bone metabolism by inhibiting the proliferation of osteoplasts and fibroblasts,[79] resulting in attachment loss and bone resorption. Also, the levels of mediators of bone resorption, such

as Osteoprotegerin (OPG) and Receptor Activator of Nuclear factor kappa B Ligand (RANKL), are increased in the Gingival Crevicular Fluid of patients with poorly controlled diabetes and periodontitis compared with patients with periodontitis and well-controlled diabetes or even systematically healthy with periodontitis. These elevated values of RANKL and OPG help explain the enhanced alveolar bone destruction in diabetic patients.[80] Another factor that can influence the inflammatory state of the periodontal tissue is that altered oxidative metabolism in diabetes also results in dyslipidemia, which is associated with increased lipid peroxidation and thus may exacerbate microbially triggered inflammation. A significant correlation was found between markers of lipid peroxidation in plasma and sulcular fluid in the diabetes group and periodontal parameters, and a positive association between levels of lipid peroxidation and levels of inflammatory cytokines in gingival crevicular fluid.[81] Overall, there is a lot of strong evidence in the literature that diabetes mediated by hyperglycemia and AGEs has an impact on periodontal inflammation.[82] Figure 2 shows an overview of the possible mechanisms in which diabetes can cause the progression of periodontal disease

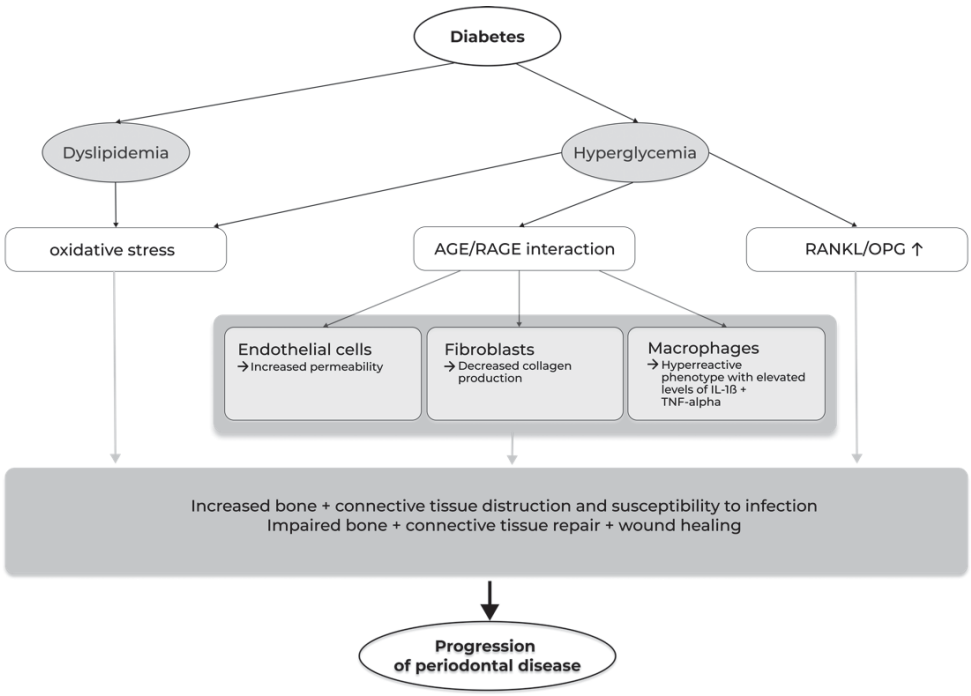

Fig. 2: **Influence of Diabetes mellitus on Periodontal Disease progression.** Modified by Polak et al.[82]

3.3 Possible impacts of periodontal disease on diabetes mellitus

As our data show, the risk of developing diabetes was elevated by 26% for patients with periodontitis, the mechanisms by which periodontal disease can negatively affect diabetes should be discussed in more detail. Just as a hyperglycemic state can influence the subgingival inflammatory response, the periodontal microbiome has conversely been shown to be related to increased tissue insulin resistance.[83] This is caused by metabolic and degradation products, such as lipopolysaccharides from bacteria in periodontal pockets, which enter the systemic circulation via the blood supply. Through various signaling cascades, they lead to increased levels of pro-inflammatory cytokines such as interleukins and TNF-alpha, which enhance insulin resistance.[84,85] A dose-response relationship between the severity of periodontitis and serum levels of TNF has been demonstrated.[86] In this context, it was also shown that antimicrobial periodontal treatment led to a reduction in serum TNF levels and correlated with an improvement in glycemic control in people with diabetes.[87] Periodontitis is thought to alter the metabolic status of diabetics inducing an increase in diabetes-associated complications. In one study, 82% of the people with diabetes and periodontitis suffered severe cardiovascular events compared to only 21% of individuals with diabetes but without periodontitis.[88] In summary, there is little mechanistic evidence in the literature to date of the influence of periodontitis on the disease pathways of diabetes and more research is needed in the future to investigate this issue, involving both microbial assessment and analysis of cytokine levels.

3.4 Methodological Aspects

3.4.1 Assessment of periodontal disease

In the risk of bias assessment, an important focus was on the method used to diagnose periodontitis, as there was substantial variation between studies. Superiorly three different methods can be distinguished: the purely self-reported diagnosis, the assessment of various clinical parameters and a combination of

these two. In the risk of bias analysis of the included studies, they were classified with high risk of bias in the category assessment of periodontal disease, if the diagnosis was derived from self-reports. However, in the subgroup meta-analysis, no differences emerged between the different qualities in the diagnostic survey. However, the number of studies here is too small to obtain a meaningful result.[68] The meta-analysis by Nascimento et al.[60], showing an 86% increased incidence and progression of periodontitis in patients with diabetes, indicates a 23% heterogeneity between studies by the criteria used to determine the presence of periodontitis. Self-report is an efficient tool for the assessment of many diseases, but its validity with regard to periodontal diseases has not yet been adequately investigated. As a systematic review on this of validation studies showed variation regarding the reported question and its phrasing. Good validity for the assessment of periodontal disease was shown, for example, for the question whether a subject has ever been told by a dentist that he has deep periodontal pockets. This resulted in a sensitivity of 55%, a specificity of 90% and a positive predictive value of 77% against clinical measurements of pocket depth.[89]

Thus, in the future, to appropriately integrate self-reports into studies, questions that have been tested with high validity against standard clinical measurements should be used selectively and additional multiple questions should be used in combination. This could allow larger epidemiological studies to be conducted more cost-effectively without underestimating the prevalence of periodontal disease. A wide variance in the prevalence and extent of periodontal disease has been observed in epidemiologic studies, which is largely related to the different methods of data acquisition and the case definition of how the disease is defined.[44] Over the years, many different diagnostic criteria have been used such as the collection of PPD,[66] CAL,[65] radiographic bone loss[90] but also tooth loosening[91]. Furthermore, there has not been a uniform threshold and number of sites that have these values to determine the presence of the disease.[49] This generally leads to a lack of uniformity and poor comparability of results among studies.[44,92] So despite the fact that CAL was considered the gold standard in diagnosis of periodontal disease, since the 1989 World Workshop in Clinical

Periodontics,[41] only a few studies have used it as a diagnostic tool and instead have applied other classification systems and case definitions. This heterogeneity in the establishment of the case definition also causes the problem of either underestimation or overestimation of disease prevalence.[92] As periodontitis is characterized as inflammation leading to loss of periodontal attachment, it is clinically detected by circumferential evaluation of the teeth using standardized periodontal probes from the cementoenamel junction to the deepest point of the periodontal pocket.[43] CAL has become the gold standard in clinical diagnostics because the cementoenamel junction as reference point is invariant, compared to the PPD measurement, whereas the reference point is the gingival margin, which changes with the state of inflammation.[93] In addition, a study showed that the prevalence of moderate (4-6mm) and deep (> 6mm) periodontal pockets remained approximately stable after 34 years of age, indicating a weak correlation between increasing age and PPD. In contrast, however, the proportion of moderate (4-6mm) and severe (> 6mm) CAL increases steadily with age.[45] Because PPD is measured from the gingival margin, recession (REC) of the gingival margin can occur to a similar extent as loss of apical attachment. Despite progressive periodontal destruction, consistent PPD values can be measured as gingival REC occurs over time,[94] making PPD and CAL unrelated, particularly with advancing age. Thus, clinical measurements of PPD alone may lead to an underestimation of periodontitis and are not considered sufficient to determine the extent of periodontal disease.[44] But REC presents a complication in interpreting measurements of PPD and CAL because attachment loss may be due to periodontal pocketing, gingival REC, or a combination of both.[95] In a study of older adults who developed attachment loss of > 3mm over a period of time, 58% experienced increased PPD and 42% experienced gingival REC.[95] Thus, the use of CAL values alone may lead to periodontally healthy sites being declared as diseased sites, as attachment loss may also be due to non-inflammatory gingival REC.[44] Figure 3 shows the differences in the measurements of PPD, CAL and gingival REC.

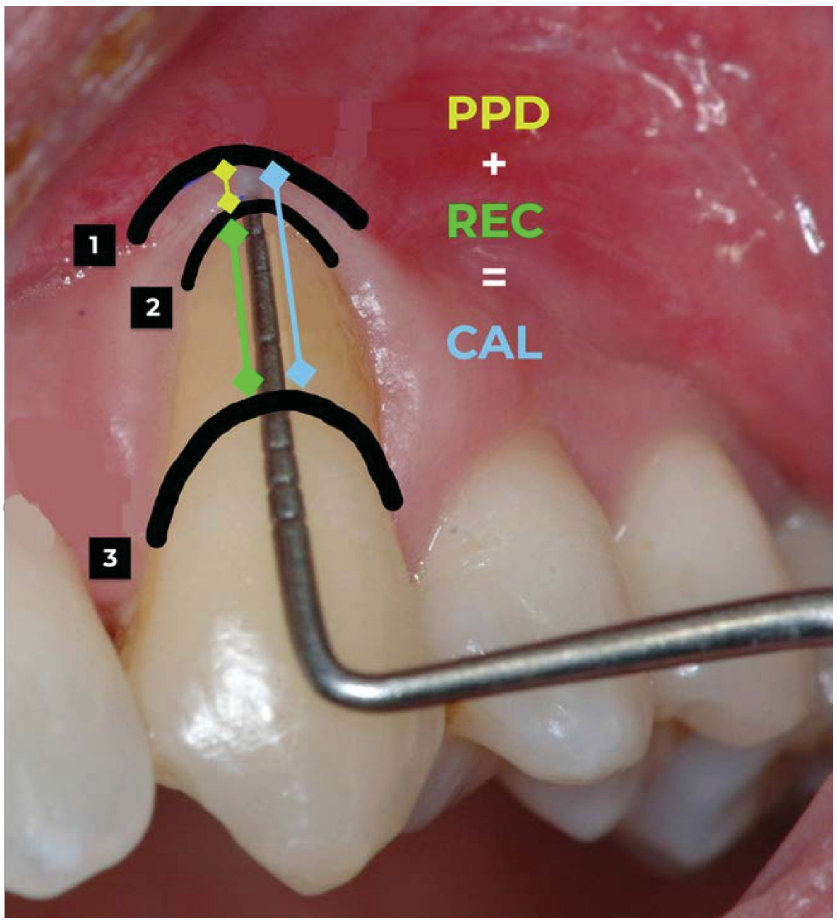

Fig. 3: **Clinical measurements of PPD, REC and CAL:** 1) Base of a periodontal pocket 2) Gingival margin 3) Cementoenamel junction. Modified by Cafiero et al.[96]

Another problem with surveying measurements is that there can be deviating measurements between different practitioners but also in repeated measurements by the same practitioner. An overall standard deviation of approximately 0.8 mm (range 0.4 to 1.2 mm) was found in over 46,000 repeated measurements of periodontal sites in 58 patients.[97] A decisive factor for the deviations is the force with which the probe is guided into the periodontal site during the measurement. If the force is too high, the probe tip can be shifted over the junctional epithelium in an inflamed pocket and a higher value for CAL can be obtained than is actually the case.[97,98] Another study showed that the determination of the coronal location of the connective tissue attachment varies depending on the inflammatory state of the gingiva and that if this is not taken into account and the applied force, which should be approximately 25 grams, is not standardized, scattering of the measured values can occur up to 2 mm.[99]

These problems with the respective measurements provide the basis for combining measurements of CAL and PPD in defining a periodontitis case.[44] Many studies have established their own case definitions based on different combinations of CAL, PD and bone loss, without consensus on criteria for the diagnoses. Thus, thresholds for each clinical parameter must be established for a site and the number of sites that must be affected to establish disease. The choice of thresholds must be made critically, as the slightest change will lead to wide variation in prevalence values.[100] In 2003, the CDC/AAP developed a standardized clinical case definition for population-based studies of periodontitis.[44]

Disease category	**Clinical definition**		
Mild periodontitis	≥ 2 interproximal sites with CAL ≥ 3 mm (not the same tooth)	and or	≥ 2 interproximal sites with PPD ≥ 4 mm (not the same tooth) 1 site with PPD ≥ 5 mm
Moderate periodontitis	≥ 2 interproximal sites with CAL ≥ 4 mm (not the same tooth)	or	≥ 2 interproximal sites with PPD ≥ 5 mm (not the same tooth)
Severe periodontitis	≥ interproximal sites with CAL ≥ 6 mm (not the same tooth)	and	≥ 1 interproximal site with PPD ≥ 5mm

Table 1: **Case definition of periodontitis by the CDC/AAP[44,101]**

The inclusion of interproximal sites is important because this is where periodontal destruction begins and is usually most pronounced. Furthermore, gingival REC affects measurements less here than, for example, at buccal sites of the tooth.[94] The threshold value of CAL was set at 6 mm, as the mean distance from cementoenamel junction to alveolar ridge is 1.0 mm with a range of 0.04 to 3.36 mm.[102] Since it must be taken into account that the probe tip is advanced above the pocket base in inflamed tissue and the standard deviations of the measurements are approximately 1 mm, a lower threshold could include healthy sites. Also, the threshold should be measured on at least two different teeth to reduce false diagnoses, as local factors such as overhanging crown margins or proximal caries may generate isolated attachment loss that does not reflect the

overall periodontal status of a patient.[103] Some studies used indexes as case definitions such as the PI.[64] The problem with this is that it is a purely visual surveyed index, which leads to the problem that there are strong variations in the survey between different examiners, especially in the early stages of the disease.[48] It is also flawed that gingivitis has been evaluated as synonymous with early periodontitis, with the assumption that any gingivitis will develop into periodontitis.[38] Therefore, although this index has been used in many epidemiological studies, it is no longer considered valid.[44] In our risk of bias analysis, studies whose periodontitis diagnosis was based on the PI were considered partially appropriated in this republic and thus with moderate risk of bias.[68] The WHO has created a periodontal scoring index to enable surveillance of oral health across countries.[104] This CPI is characterized by its easiness and reproducibility and has therefore been used in many clinical studies. However, because it is based solely on PPD and inflammatory symptoms, it does not adequately measure the extent and severity of periodontitis.[47] Since untreated periodontitis leads to progressive destruction of the tooth supporting tissues with resorption of the alveolar bone, tooth loss can be expected as long-term consequence.[105] That is why several studies used tooth loss as marker for the presence of periodontal disease.[23,106,107] Tooth loss can be considered as an indicator of periodontal disease, as it has been demonstrated that there is a correlation between increasing number of lost teeth and an age-adjusted progression of PPD and enhanced CAL.[67] However, although periodontitis is one of the leading causes, caries is still considered to be the most common reason for tooth loss.[108] Therefore, future studies should not use the presence of tooth loss as a diagnostic parameter for the presence of periodontal disease. Due to the existing problems in measuring clinical parameters of periodontitis, there is increasing research to find markers for periodontitis that are independent of it. Gingival crevicular fluid, the exudate of the dental sulcus or periodontal pocket, is intended to be used for non-invasive tests to detect periodontal disease activity through biochemical analysis.[100] It is in the experimental phase to establish inflammatory markers in the gingival crevicular fluid, which are expressed as a host response to inflammation, as a reliable measure of periodontitis.[109] The

activity of inflammatory markers lead to increased flow of gingival crevicular fluid, which is due to increased permeability of the vessel walls. Thus, the volume and composition of the fluid changes with the state of inflammation.[110] Inflammatory mediators such as Prostaglandin E2 (PGE2), TNF-alpha and IL-1ß have been shown to be associated with active periodontitis and have an important role as mediators of local tissue destruction. For instance, one study showed that mean IL-1ß and PEG2 levels in the gingival crevicular fluid are strongly positively associated with clinical signs of periodontitis and are thus higher in patients with higher levels of PPD.[111] However, it is still difficult to quantify this association and determine the exact level at which the cytokine is expressed.[112] Although gingival crevicular fluid is a promising medium for future diagnostics, it has been difficult to provide a chairside diagnostic medium because sample collection is technically demanding and requires expensive and time-consuming laboratory processing.[113] More research is needed in the future to improve these diagnostic methods in clinical use and more studies on the validation of the methods in relation to previous diagnostic methods such as the assessment of PPD and CAL are needed to gain acceptance by dentists.[112]

3.4.2 Assessment of diabetes mellitus

The second focus in the risk of bias assessment of the original studies is the method by which the diagnosis of diabetes was derived. Here, the diagnosis was evaluated either by self-report, diagnoses based on blood tests or ICD codes and records from hospitals or insurance database. Diagnoses by blood test also differed in the included studies, either the plasma glucose criterion was used (FPG or the 2-h plasma glucose value after a 75-g oral glucose tolerance test) or HbA1c values.[68] Nascimento et al.[60] found in their meta-analysis that the relative risk of periodontal disease was lower when the diabetes diagnosis was made by self-report than when it was based on blood tests. In our subgroup analysis, however, no relevant differences were found, which should be viewed critically, as the number of studies is too small to make a valid statement.[68] A study examining the correspondence between self-reported diabetes and medical record evidence found that when diabetes was reported, it was confirmed by

medical records in 92% of cases, giving a very high positive predictive value. In addition, it was found that most false positives were due to errors in filling out the questionnaires.[114] . Overall, this shows that diabetes mellitus is in general one of the self-reported outcomes with the highest validity.[115] According to the ADA, the different blood tests such as plasma glucose levels and HbA1c levels are equally appropriate tests for detecting diabetes. Nevertheless, it should be taken into account that the 2-hour plasma glucose test has been shown to diagnose more patients with diabetes compared to the fasting glucose test and HbA1c test.[11] Diagnosis by HbA1c has the advantage of being easier to perform, but the 6.5% cut-off has been shown to identify one-third fewer cases than a fasting blood glucose cut-off of 126 mg/dl.[116] It is important to consider that A1c is an indirect measure of average blood glucose concentration and therefore other factors such as age, ethnicity and anemia may also influence hemoglobin glycation.[11,117] In order to achieve better comparability among the studies and thus more accurate results, more uniform methods for ascertaining the diagnosis of diabetes in studies should be chosen in the future.

Regarding the type of diabetes, of the 15 included studies, nine studies[64,66,91,118-123] focused on Type 2 diabetes and only one study on Type 1.[124] It is problematic that in five studies[65,125-128] there is no further differentiation according to type of diabetes or both were combined (one of them showed separate results). While one meta-analysis[129] found a significant association for periodontitis and type 2 diabetes but none for type 1, our subgroup analysis found no significant differences here. However, the number of studies is too small to make a meaningful statement. The meta-analysis of Chàvarry et al.[129] attributes the lack of association between periodontitis and type 1 diabetes to the fact that the age of the study population in type 1 diabetes is between 11 and 15 years, and the prevalence of periodontitis only increases significantly after 30 years of age. The advantage of our analysis is that we excluded studies with participants under 18 years of age. However, the study in which only patients with type 1 diabetes were examined states that the participants are < 40 years of age and therefore it is not possible to determine whether adolescents are also included.[124] Also in the studies combining type 1 and type 2 diabetes, the participants in two studies[65,128]

are also under 30 years of age, while in the studies investigating only type 2 diabetes, only one study[64] has participants under 30. It has been shown that the prevalence of periodontitis is highest in the age group 44-49 years, but also tends to decrease at higher ages due to a higher number of edentulous people.[52] That fact may again distort the results, as periodontitis may have led to tooth loss. Thus, in future studies of the association between periodontitis and diabetes, the age of the study population should be selected more carefully to avoid bias.

3.5 Strengths and limitations

The strengths of this report include the fact that the work follows a preregistered protocol and the established reporting guidelines. In addition, a comprehensive systematic literature search was conducted by independent investigators and the risk of bias was assessed using a validated tool from Cochrane collaboration. Only prospective studies were included in the meta-analysis, so that a time course of the disease is presented, and a clear statement can be made about which disease was present first and which developed during the observation period. In addition, we examined and presented both directions of the association of the diseases separately. We also conducted dose-response meta-analyses for each possible association. On the other hand, there are also limitations in this report, which are mainly due to the heterogeneity of the assessment methods of periodontitis and diabetes in the individual studies, as has already been discussed above in detail. However, to identify possible sources of variability between studies, subgroup analyses were conducted that did not show considerable differences. Another weakness is the study design of the included studies, as they are observational studies. Thus, no statement can be made as to whether the relationship is causal or whether the two diseases only exist in parallel and share the same risk factors. Residual confounding can therefore not be completely excluded. In addition, no repeated measurements and thus, changes in the course of the disease could not be taken into account.

3.6 Future clinical relevance

Our systematic review and meta-analysis of the bidirectional association between periodontitis and diabetes is intended to improve dentists' understanding of the risks of the systemic effects of periodontal disease, to better communicate this association to their patients, and to highlight the importance of interdisciplinary collaboration between dentistry and general practice in clinical practice. The aim is to provide better awareness and multidisciplinary care for patients suffering from periodontitis and diabetes and to prevent one disease from worsening the other, if left untreated. Our results show that patients with periodontitis have a higher risk of developing diabetes. Given the high prevalence of periodontitis of adults worldwide and that the disease is easily treated when diagnosed, shows the great potential and opportunity for improving public health implications. An important step for collaboration between different healthcare professionals could be screening for diabetes but also prediabetes in dental practices. One study screened dental patients, who were unaware of their diabetes status, for diabetes using a HbA1c chairside test and the diabetes risk test from the ADA.[130] About 41% of the patients had an HbA1c level of 5.7% or higher and were therefore referred to a doctor for further diagnosis. Of them, 12% were diagnosed with diabetes, while another 23% had prediabetes. Even identifying people with prediabetes can help to start early interventions to eliminate risk factors for diabetes and its complications, such as quitting smoking or increasing physical activity.[130] In one study, dental examination with assessment of various periodontal clinical parameters combined with point-of-care HbA1c testing was able to detect 92% of true diabetes cases.[131] Thus, the dental practice with its regular check-up visits is a good way not only identify diabetes cases, but also to monitor blood glucose levels. This is also shown by the fact that among people over 65 years of age, about 58% had at least one dental appointment per year, but only 38% had an appointment with their family doctor.[132] It was also revealed that blood glucose testing in dental practices is well accepted by patients and dentists, as 93% of dentists thought the test was necessary and 83% of patients thought the test was a good idea.[133] In addition, it should be noted that the literature show that the severity of periodontitis increases the risk of diabetes-

associated complications and there is a significantly higher all-cause mortality in patients with diabetes and periodontitis, compared to people only suffering from diabetes.[134] A meta-analysis from 2017 examined the effect of non-surgical periodontal therapy on metabolic control in diabetic patients and demonstrated a significant reduction in HbA1c values from -0.27% to -1.03%, 3 months after therapy. This improvement in glycemic control highlights the impact that periodontal therapy can have on systemic health in patients with diabetes and the importance of early detection and treatment of periodontitis in diabetic patients.[135] If the magnitude of HbA1c- value reduction, achieved shortly after periodontal therapy can be maintained over time, this could have a positive impact on potential complications of diabetes and lead to a reduction in diabetes-associated mortality in the long term. It is therefore of great importance that dentists also have the knowledge to identify patients at high risk of developing diabetes or who may be suffering from undiagnosed diabetes.[132] On the other hand, it is also the case that physicians are not educated enough about periodontal disease and do not inform their patients about the connection between diabetes and oral health. This fact can be illustrated by a study that reported that only 18% of patients with diabetes are aware of its impact on oral health.[136] In summary, guidelines for physicians and dentists on the management of patients with diabetes and/or periodontitis have been developed by the International Diabetes Federation and European Federation of periodontology.[134] Physicians are advised to educate their patients with diabetes about oral health and their increased risk for periodontitis and to make them aware of the negative impact of untreated periodontitis on diabetes control. It is recommended as standard practice that every patient diagnosed with diabetes should be screened for oral or periodontal changes by asking for symptoms with questionnaires or visual assessment of the mouth and should be referred to a periodontal examination by a dentist. If the patient has already been diagnosed with periodontal disease, the physician should help to ensure that the periodontal condition is regularly checked and treated. The dental guideline states that patients without a previous diabetes diagnosis but with existing periodontitis should be educated about risk factors for diabetes and the relationship between

the two conditions.[134] A questionnaire can be administered directly to determine the risk for possible diabetes and, if risk factors or symptoms are present, referral can be made directly to a clinician for further diabetes diagnosis. If, on the other hand, the patient already suffers from diabetes, the dentist should inquire about the diabetes control and assist doctors in educating them about the proper management of the disease and help to ensure that the patient has his or her blood glucose control monitored regularly.[130,134]

3.7 Conclusions

The findings of the systematic review and meta-analysis show a positive bidirectional association between periodontal disease and diabetes mellitus. These results support current guidelines, stating that the dental office can be important for an early detection of diabetes mellitus and that individuals with diabetes mellitus should be informed about their higher risk of developing periodontal disease. To provide clearer statements about the association of the two diseases in the future, the currently valid, uniform diagnostic criteria and threshold values should be used in studies in order to obtain comparable results.

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Appendix

Supplemental Material

Bidirectional association between periodontal disease and diabetes mellitus: A systematic review and meta-analysis of cohort studies

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Table S1. Search term

a) Pubmed (all fields)
((periodontal OR periodontitis OR "periodontal disease" OR “clinical attachment loss”) AND (diabetes OR Hba1c OR HbA1c OR A1c OR glycated OR glycosylated OR glucose OR "Glycated Hemoglobin A"))
b) Web of Science (title, abstract, author keywords, keywords plus®)
TOPIC: (((periodontal OR periodontitis OR "periodontal disease" OR “clinical attachment loss”) AND (diabetes OR Hba1c OR HbA1c OR A1c OR glycated OR glycosylated OR glucose OR "Glycated Hemoglobin A")))

Table S2. Quality assessment using the Quality in Prognosis studies (QUIPS) tool.

Signalling question	**Authors‘ judgement for `yes**
Study participation: yes/no/unclear/NA (not applicable)	
a) Adequate participation in the study by eligible people	1) men and women ≥18 years without diabetes at baseline are eligible or 2) men and women ≥18 years without periodontal disease at baseline are eligible
b) Description of the source population or population of interest	Source population or population of interest is clearly described (e.g. region, age ...)
c) Description of the baseline study sample	Baseline study sample is clearly described
d) Adequate description of the sampling frame and recruitment	Recruitment, selection criteria and key characteristics of the source population are clearly described
e) Adequate description of the period and place of recruitment	Time period and place of recruitment are clearly described
f) Adequate description of inclusion and exclusion criteria	Inclusion and exclusion criteria are clearly described and presented.
Study participation: risk of bias rating (low/moderate/high/unclear)	**Low**: The study sample represents the population of interest and sufficient information on the recruitment and the selection process and the key characteristics of the population is available. **Moderate:** The study sample represents the population of interest but some information on the recruitment and/or the selection process and/or the key characteristics of the population were not described. **High:** The study sample does not represent the population of interest and/or insufficient information on the recruitment and the

	selection process and the key characteristics of the population is available. **Unclear:** not sufficient information were provided to judge this domain.
Study attrition: Yes/no/unclear/NA	
a) Adequate response rate for study participants	Response rate was adequate: ≥80% (<5 years) or ≥70% (≥5 years)
b) Attempts to collect information on participants who dropped out described	Attempts to collect information on participants who dropped out are described (e.g. telephone contact, mail, registers)
c) Reasons for loss to follow-up provided	Information about the reason participants were lost to follow-up are set up (e.g. deceased participants, participants refused or moved)
d) Adequate description of participants lost to follow-up	Key characteristics of participants lost to follow-up are described (Age, sex, diabetes status/ periodontal status at baseline)
e) No important differences between participants who completed the study and those who did not	No important differences in baseline characteristics between responders and non-responders
Study attrition: risk of bias rating (low/moderate/high/unclear) **Note:** In this domain, the first item was rated as the most important and thus decisively weighted	**Low:** If loss of follow-up was low and/or loss to follow-up was not associated with key characteristics and no potential bias of the observed association between the prognostic factor and the outcome is expected. **Moderate:** If loss of follow-up was low but not sufficient information were provided to judge if remaining loss of follow-up was associated with key characteristics, and thus, potential bias of the observed association between the prognostic factor and the outcome cannot be ruled out completely. **High:** If loss of follow-up was high and loss to follow-up was associated with key characteristics and potential bias of the observed association between the prognostic factor and the outcome is expected. **Unclear:** not sufficient information were provided to judge this domain.
Prognostic factor measurements: yes/no/unclear/NA	
a) Clear definition or description provided	1) Clear definition of periodontitis has been set by clinical oral examination (e.g. measurements of PPD or CAL) or

	2) Clear definition of diabetes mellitus has been set by blood laboratory measurements (e.g. FPG, HbA1c values)
b) Adequately valid and reliable method of measurement	1) Valid and reliable methods of assessment for periodontitis include measurements of CAL or PPD and can be presented by Community Periodontal Index; We consider self-reported diagnosis that is validated by a physician and ICD-Codes from health insurance data as partial valid and reliable; Percentage of radiographic bone loss or self-reported periodontal disease or self-reported symptoms of periodontal disease without validation are not reliable; Technique for measurements of periodontal status is well described and measurements were performed by a dentist 2) Measurements of blood glucose or HbA1c levels are valid and reliable methods of measurement for diabetes mellitus; Self-reported history of diabetes with validation of the diagnosis by a physician and information from medical records are partial reliable; Only self-reported diagnosis without validation by a physician is not considered a valid and reliable method of measurement; Technique for laboratory measurements is well described.
c) Continuous variables reported or appropriate cut points used	1) Standard cut points for diagnosis of periodontitis: Probing pocket depth ≥ 4mm which corresponds to Community Periodontal Index code ≥ 3; clinical attachment loss: 1-2mm (mild); 3-4mm (moderate); ≥5mm (severe) or 2) Standard cut points for diagnosis of diabetes mellitus: Fasting plasma glucose ≥ 126 mg/dL or HbA1c >6,5%.
d) Same method and setting of measurement used in all study participants	1) Measurements of periodontal status are the same for all study participants 2) Measurements of glycemic status are the same for all study participants.
e) Adequate proportion of the study sample had complete data	Number in final model with complete data
f) Appropriate methods of imputation were used for missing data	Complete case analysis for exposure and outcome variables are required. If the analysis was almost complete case analysis, imputation was not required
Prognostic factor measurements: risk of bias rating (low/moderate/high/unclear)	**Low:** The prognostic factor of interest is adequately defined and measured in an

	adequate proportion of the study sample to sufficiently limit potential bias. **Moderate:** The prognostic factor of interest is partly adequately defined and measured in an adequate proportion of the study sample **High:** The prognostic factor of interest is not adequately defined and/or measured and/or missing in a substantial proportion of the study participants leading to potential bias. **Unclear:** not sufficient information were provided to judge this domain.
Outcome measurement: yes/no/unclear/NA	
a) Clear definition of the outcome provided	1) Clear definition for the diagnosis of diabetes mellitus has been set (e.g. FPG levels, HbA1c values) 2) Clear definition for the diagnosis of periodontitis has been set (e.g. PPD or CAL levels)
b) Use of adequately valid and reliable methods of outcome measurement	1) Valid and reliable methods of assessment for periodontitis include measurements of CAL or PPD and can be presented by Community Periodontal Index; We consider self-reported diagnosis that is validated by a physician and ICD-Codes from health insurance data as partial valid and reliable; percentage of radiographic bone loss or self-reported periodontal disease without validation are not reliable; Technique for measurements of periodontal status is well described 2) Measurements of blood glucose or HbA1c levels are valid and reliable methods of measurement for diabetes mellitus; Self-reported history of diabetes with validation of the diagnosis by a physician and information from medical records are partial reliable; Only self-reported diagnosis without validation by a physician is not considered a valid and reliable method of measurement; technique for laboratory measurements is well describe
c) Use of same method and setting of outcome measurement in all study participants	1) Measurements of type 2 diabetes mellitus are the same for all study participants or 2) Measurements of periodontal disease are the same for all study participants
Outcome measurement: risk of bias rating (low/moderate/high/unclear)	**Low:** The outcome of interest is adequately defined and measured in an adequate

	proportion of the study sample to sufficiently limit potential bias. **Moderate:** The outcome of interest is partly adequately defined and measured in an adequate proportion of the study sample **High:** The outcome of interest is not adequately defined and/or measured and/or missing in a substantial proportion of the study participants leading to potential bias. **Unclear:** not sufficient information were provided to judge this domain.
Study confounding: yes/no/unclear/NA	
a) Measurement of all important confounders	Minimal adjusted models should include: Age, sex, socio-economic status, smoking and BMI as most important confounders
b) Provision of clear definitions of the important confounders measured	Measurements of confounders are described and defined
c) Adequately valid and reliable measurements of all important confounders	Measurements of confounding factors are valid and reliable (e.g. validated questionnaires, examination by trained personal, etc.)
d) Use of the same method and setting of confounding measurement in all study participants	The method and setting of confounding measurement are the same for all participants
e) Appropriate imputation methods used for missing confounders (if applicable)	Appropriate methods of imputation for missing covariate data are applied and described.
f) Important potential confounders were accounted for the study design	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, use of multivariable analysis etc.).
g) Important confounders were accounted for in the analysis	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).
Study confounding measurement: risk of bias rating (low/moderate/high/unclear) **Note:** Confounding is expected in all observational studies, because residual confounding cannot be completely excluded. Thus, for the item a) no study was assigned with “yes” and the total domain cannot be rated higher than moderate	**Low:** Important potential confounders were appropriately accounted for, and no potential bias of the observed association between the prognostic factor and the outcome is expected. **Moderate:** Studies adjusted for the defined minimal adjustment set and confounders were adequately defined and measured to sufficiently limit potential bias. **High:** Studies did not adjust for the defined minimal adjustment set and/or confounders were adequately defined and measured leading to potential bias. **Unclear:** not sufficient information were provided to judge this domain.
Statistical analysis and reporting: yes/no/unclear/NA	

a) Sufficient presentation of data to assess the adequacy of the analytic strategy	There is sufficient presentation of data to assess the adequacy of the analysis (e.g. findings are displayed in a table or in the text). The results are expressed as risk ratios (e.g. hazard ratios, relative risks, odds ratios) with corresponding 95% confidence intervals
b) Strategy for model building is appropriate and based on conceptual framework model	The selection of the confounders are described and appropriate (e.g. literature-based); step-wise regression is not appropriate
c) Statistical model is adequate for the study design	Multivariable logistic regression or cox proportional hazard model are applied. Univariate methods are not appropriate.
d) No selective reporting of results	There is no selective reporting of results (e.g. findings are shown for a specify age group, time period etc.)
Statistical analysis and reporting: risk of bias rating (low/moderate/high/unclear)	**Low:** The statistical analysis was appropriate and the data are sufficiently reported. **Moderate:**. The statistical analysis was appropriate but the strategy for model building is not adequately described and/or for the main findings there is no selective reporting of the data. **High:** The statistical analysis was not appropriate and/ or there is selective reporting of the data. **Unclear:** not sufficient information were provided to judge this domain.

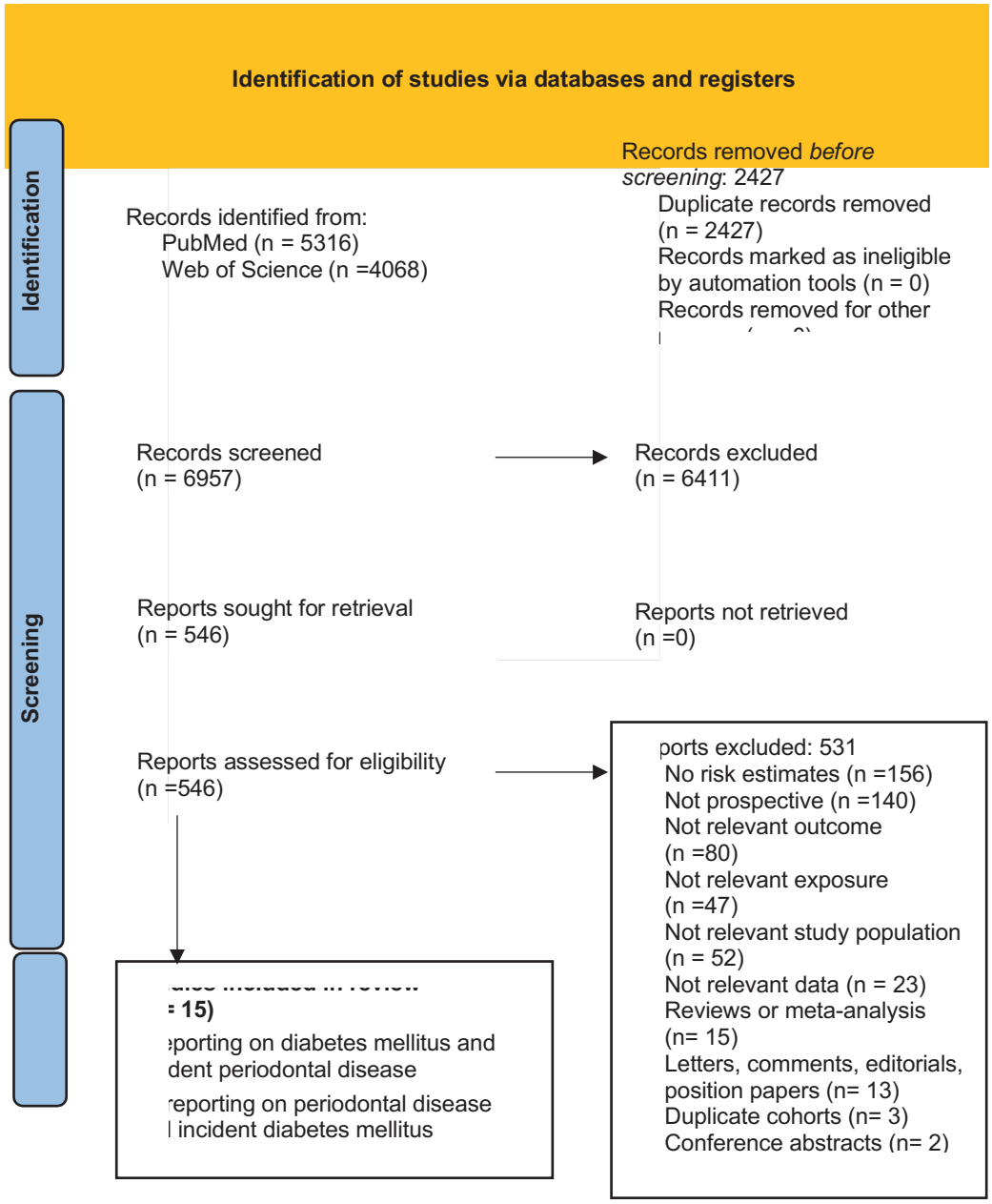

Figure S1. Flow chart of the study selection process

Template from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Table S3. Excluded studies based on full-text screening

Exclusion criteria	**Excluded studies**
No risk estimates (studies that do not have a risk ratio of the association of periodontal disease and diabetes mellitus)	[1-156]
Not prospective (cross-sectional studies, case-controls studies, no prospective associations)	[157-296]
Not relevant outcome (studies that do not have an indicator of periodontal disease or diagnosis of diabetes mellitus as outcome)	[297-376]
Not relevant study population (e.g. studies in children and adolescents, pregnant women)	[377-428]
Not relevant exposure (studies that do not have an indicator of periodontal disease or diagnosis of diabetes mellitus as exposure)	[429-475]
Not relevant data (studies that do not have a relevant exposure and outcome)	[476-498]
Systematic reviews/Meta-analysis	[499-513]
Letter, comments, editorials, position paper	[514-526]
Duplicate cohorts	[527-529]
Conference abstracts	[530, 531]

Table S4. Study characteristics of cohort studies included in the meta-analysis

First author, publication year, country	Study design, Study name or description, Follow-up	Sex, age	Number of participants, number of cases	Exposure, exposure assessment	Exposure categories	Outcome, outcome assessment	Relative Risk (95% CI)	Adjustment for confounders
Studies of diabetes mellitus and incident periodontal diseases								
Alshihayb et al., 2020 USA[532]	Prospective cohort study, Veterans Affairs (VA) Dental Longitudinal Study (DLS) is a subset of the VA Normative Aging Study (NAS), 14 y	Men, 58.9y	521, 264	Type 2 diabetes, existing NAS medical records	Diabetes yes/no	Incident periodontal Disease (severe), Clinical periodontal examinations: probing pocket depth at multiple sites per tooth & attachment loss	1.32 (0.77; 2.26)	Time-varying age, education, time-varying body mass index, time-varying comprehensive smoking index
Chiu et al., 2015, Taiwan[533]	Prospective cohort study, Keelung community-based integrated screening (KCIS) program, 5 y	Women and men, 35-44 y	4387, 1247	Type 2 diabetes, Fasting plasma glucose (FPG) or self-reported type 2 diabetes	FPG normal (<100 mg/dL), Type 2 diabetes (≥126 mg/dL)	Incident periodontal disease, measurement of periodontal pocket depth (PPD) and classified by Community Periodontal Index (CPI)	1.95 (1.22; 3.13)	Age, gender, years of education, betel nut chewing, smoking, alcohol consumption, waist, triglyceride, HDL, elevated blood pressure, fruit intake, physical activity
Jimenez et al., 2012, USA[534]	Prospective cohort study Health Professionals Follow-Up Study (HPFS), 20 y	Men, 40-75 y	35247, 3009	Type 2 diabetes, self-reported: 1) ≥1classic symptom of diabetes and FPG of ≥140mg/dl (cases reported after 1996: ≥ 126mg/dl), non-FPG ≥200mg/dl ; or 2) elevated plasma glucose concentrations on at least two different occasions in the absence of symptoms; or 3) hypoglycemic	Diabetes yes/no	Periodontal disease, Self-reported	1.29 (1.13; 1.47)	Age, gender, smoking status, BMI, fruit/vegetable intake, number of teeth at baseline, physical activity, alcohol consumption, dental profession, baseline history of stroke, coronary artery bypass surgery or myocardial infarction

Morita et al., 2012, Japan[535]	Prospective cohort study, Participants in this study worked in and around Nagoya City and had annual health check-ups between December 1997 and February 2006, 5 y	Women and men, 30-69 y	5856, 2068	HbA1c level, measured in a fasting venous blood sample	Diabetes: no (HbA1c < 6,5%), Diabetes: yes (HbA1c ≥ 6,5%)	Periodontal disease, The PPD around 10 index teeth were examined to obtain the CPI	1.17 (1.01; 1.36)	Age, gender, smoking status, BMI
Lee et al., 2018, South Korea[536]	Prospective cohort study, National Health Insurance Service-Elderly Cohort (NHIS-EC), 11 y	Women and men, ≥ 60 y	149785, N.A.	Type 1 and 2 diabetes, ICD-10 codes: E101, E105, E109, E111, E115, E119, E131, E135, E139, E141, E145, E149	Diabetes yes/no	Periodontal disease, based on the guidelines of the Centers for Disease Control and American Academy of Periodontology using dental history questionnaires, clinical signs, and an oral examination and radiographic evaluation: diagnosis of PD by ICD-10 ([K052],[K053],[K054], [K055], [K056]) and who received periodontal treatment	1.18 (1.17; 1.20)	Age, gender, household income, insurance status, residence area, health status and other chronic diseases
Lee, et al., 2019, Taiwan[498]	Prospective cohort study, National Health Insurance database Taiwan (NHIRD), Approx. 9 y	Women and men, >20 y	78768, 15170	Mainly type diabetes 2, ICD-9 codes 250 and 251, but diagnosis after age of 20 years	Mainly type 2 diabetes yes/no	Periodontal Disease, ICD-9 code: periodontitis (523.0 and 523.5)	1.04 (1.01; 1.08)	Age, sex, income, dyslipidemia, hypertension, rheumatoid arthritis, Charlson comorbidity index
Sun et al., 2018, Taiwan[537]	Prospective cohort study, National Health Insurance database Taiwan (NHIRD), 14 y	Women and men, <40 y	21240, 794	Type 1 diabetes, ICD-9 codes 250.x1 and 250.x3)	Type 1 diabetes yes/no	Periodontal disease, ICD-9 code: periodontitis (523.3 and 523.4)	1.66 (1.41; 1.96)	Age, gender, urbanization level, comorbidities of CAD, stroke, asthma, COPD, alcohol-related disease and mental disease
Studies of periodontal disease and incident diabetes								
Alshihayb et al., 2020, USA[53	Prospective cohort study, Veterans Affairs (VA) Dental Longitudinal Study (DLS)	Men, 58.9y	672, 82	Periodontal disease Clinical periodontal examinatio	No/mild vs. moderate/severe periodontal	Type 2 diabetes, medical examination interviews based on	1.33 (0.71; 2.52)	Time-varying age, education, time-varying body mass index, time-

2]	is a subset of the VA Normative Aging Study (NAS), 14 y			ns: probing pocket depth at multiple sites per tooth & attachment loss	disease	self-report		varying comprehensive smoking index .
Lin et al., 2014, Taiwan[538]	Retrospective cohort study, National Health Insurance Research Database (NHIRD), 5.47 y	Women and men, ≥ 53 y	44601, 2501	Periodontal disease, based on claims data (ICD-9-CM codes 523.4 and 523.5); needing subgingival curettage (procedure codes 91006C, 91007C, and 91008C) and periodontal flap procedure (procedure codes 91009C and 91010C)	Periodontitis needing surgical treatment no = comparison / yes = severe Periodontitis	Type 2 diabetes, patients who have been diagnosed with ICD-9-CM codes 250 at least two times and concomitantly received antidiabetic medications	1.19 (1.10; 1.29)	Age, gender, income, urbanization, hypertension, CAD, hyperlipidemia, obesity
Demmer et al, 2008, USA[539]	Prospective cohort study, National Health and Nutrition Examination Survey (NHANES I) and its Epidemi-ologic Follow-up Study (NHEFS), 17 y	Women and men, 25-74 y	9296, 817	Periodontal disease, measurement of gingival inflammation extent, the presence or absence of periodontal pockets, tooth mobility and classified by Periodontal Index (PI)	Category PI0: periodontal healthy (PI= 0); Category PI1: gingivitis (0< PI≤ 0.87); Category PI2: periodontitis (0.88≤ PI≤ 1.60); Category PI3: periodontitis (1.61≤ PI≤ 2.44); Category PI4: periodontitis (2.45≤ PI≤ 5.07); Category PI5: periodontitis (5.08 ≤ PI≤ 8.0); Edentulous	Type 2 diabetes, diabetes listed on the death certificate, self-reported physician diagnosis requiring pharmacological treatment, health care facility stay with a discharge diagnosis of diabetes	PI2: 1.03 (0.65; 1.64) PI3: 2.08 (1.51; 2.87) PI4: 1.71 (1.19; 2.45) PI5: 1.50 (0.99; 2.27) pooled to 1.64 (1.35, 1.99)	Age, gender, race, education, smoking status, BMI, physical activity, hypertension, total cholesterol, subscapular skinfold

Ide et al, 2011, Japan[540]	Prospective cohort study, worksite cohort study, 6.5 y	Women and men, 30-59 y	5848, 287	Periodontal disease, Community Periodontal Index (CPI)	no pathological pockets (CPI score: 0,1 or 2), moderate periodontitis (CPI score: 3), severe periodontitis (CPI score: 4)	Type 2 diabetes, FPG > 125 mg/dL	CPI score 3: 1.00 (0.77; 1.30) CPI score 4: 1.28 (0.89; 1.86) pooled to 1.09 (0.88, 1.35)	Age, gender, smoking status, BMI, triglyceride level, hypertension, high density lipoprotein level, gamma-glutamyl transpeptidase
Miyawaki et al.,2016, Japan[541]	Prospective cohort study, MY Health Up study, 5 y	Men, 36-55 y	2469, 133	Periodontal status, Self-reported periodontal symptoms	Tooth loosening no/yes	Type 2 diabetes, self-reported or met blood test criteria at least once during the follow-up period (FPG level ≥126 mg/dl between 2005 and 2009 and/or HbA1c values ≥ 6,5% in 2008 and 2009)	1.73 (1.14; .,64)	Age, current smoking habits, BMI, family history of diabetes, hypertension, alcohol heavy consumption (≥ 40 g/day), exercise habits (> 30min, ≥ 2 days/week)
Kebede et al.,2012, Germany[542]	Study of Health in Pomerania: SHIP-0 (baseline) and SHIP-2 (follow-up), 11.1 y	Women and men, 56.8 y	2034, 206	Periodontal disease, Periodontal measurements assessed at four sites per tooth according to the half-mouth method: 1) PPD 2) CAL	1) Mean PPD: analyzed as quartiles and continuously, 2) Mean clinical attachment level analyzed in quartiles and continuously	Diabetes, known diabetes (self-reported physician diagnoses or treatment with antidiabetic medication) or HbA1c levels ≥ 6.5% or non-FPG levels ≥11,1 mmol/L	1) Q2: 1.35 (0.82; 2.32) Q3: 1.22 (0.75; 2.00) Q4: 1.27 (0.78; 2.07) 2) Q2: 0.61 (0.36; 1.04) Q3: 0.92 (0.56; 1.49) Q4: 0.82 (0.49; 1.37) pooled to 0.78 (0.88, 1.05)	Age, gender, highest level of general education, marital status, waist circumference, physical activity, smoking status, dental visits past 12 months, follow-up time

Myllymaki et al.,2018, Finland[543]	Prospective cohort study, MY Health up study, 5 y	Women and men, 36-55 y	394, 81	Periodontal condition, Clinical oral examinations by 2 dentists: presence of deepened periodontal pockets (4mm or deeper)	periodontally healthy = No deepened periodontal pockets, PPD of 4-5 mm, PPD of ≥ 6 mm, edentulous, Number of sites with periodontal pockets 4 mm deep or deeper (continuous variable)	Type 2 diabetes, fasting venous plasma glucose ≥7,0 mmol/L and/or 2-hour venous plasma glucose ≥ 11,1 mmol/L after ingestion of 75g of an oral glucose load	PPD of 4-5 mm: 1.32 (0.69; 2.53) PPD of ≥ 6 mm: 1.56 (0.58; 1.92) pooled to 1.44 (0.93, 2.26)	Gender, risk of diabetes mellitus, physical activity, dietary habits, IGT at baseline, hypertriglyceridemia, low HDL-C, smoking status, BMI, absolute change in BMI during follow up time
Winning et al.,2017, Northern Ireland[544]	Prospective cohort study, PRIME study (Prospective Epidemiological Study of Myocardial Infarction), 7.8 y	Men, 58-72 y	1331, 80	Periodontal disease, clinical periodontal measurements: 1) PPD 2) CAL	no/mild periodontitis, moderate Periodontitis: ≥2 interproximal sites with CAL ≥4 mm, not on the same tooth or ≥2 interproximal sites with PPD ≥5 mm, not on the same tooth, severe periodontitis: ≥ 2 interproximal sites with CAL ≥6 mm, not on the same tooth, and ≥1 interproximal sites with PPD ≥5 mm	Type 2 diabetes, 1)self-reported: diabetes diagnosis, listing a medication that suggested diabetes management and 2) validated by general medical practioner: FPG ≥ 126mg/dl	Moderate periodontitis: 1.53 (0.86; 2.74) Severe periodontitis: 1.85(1.06; 3.22) pooled to 1.69 (1.13, 3.22)	Age, number of teeth, smoking status, toothbrushing frequency, marital status, baseline BMI, baseline CRP, cholesterol, history of CAD, history of hypertension, education years, dental attendance, socio-economic status
Morita et al., 2012, Japan[535]	Prospective cohort study, Participants in this study worked in and around Nagoya City and had annual health check-ups between December 1997 and February 2008, 5 y	Women and men, 30-69 y	6125, 168	Periodontal disease, The PPD around 10 index teeth were examined to obtain the CPI	CPI Code 0, CPI Code 3, CPI Code 4	Type 2 diabetes (HbA1C ≥6,5%), measured in a fasting venous blood sample	CPI score 3: 2.47 (0.78; 7.79) CPI score 4: 3.45 (1.08; 11.02) pooled to 2.91 (1.29, 6.60)	Age, gender, BMI, alcohol consumption, smoking status

Lee et al., 2017, South Korea[545]	Prospective cohort study, National Health Insurance Service-Health Examinee Cohort (NHIS-HEC), 12 y	Women and men, 40-79 y	354850, 110006	Periodontal disease, diagnosed clinically in oral checkup examinations in accordance with criteria of the Centers for Disease Control and Prevention/American Academy of Periodontology by a general dentist or a periodontitis (KCD-6 codes K05.2–K05.6, corresponding to ICD-10 codes K05.2–K05.6)	Oral healthy, Periodontal disease	Type 1 and 2 diabetes, diagnosed by physicians or other medical professionals: diabetes mellitus (KCD-6 codes E10–E14, corresponding to ICD-10 codes E10–E14)	1.16 (1.12; 1.02)	Age, gender, smoking status, income, insurance status, residence area

Table S5. Risk of bias assessment of all included studies in the meta-analysis using the Quality in Prognosis studies (QUIPS) tool.

Domains of bias: Low, moderate, high risk of bias, unclear							
Author, year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	**Overall**
Studies of diabetes mellitus and incident periodontal disease							
Alshihayb, 2020[532]	Moderate	Low	High	Low	Moderate	Low	High
Chiu, 2015[533]	Low	Moderate	Low	Low	Moderate	Low	Low
Jimenez, 2012[534]	Low	Low	Moderate	High	Moderate	Low	High
Lee, 2018[536]	Moderate	Unclear	Moderate	Low	High	Low	Moderate
Lee, 2019[546]	Low	Unclear	Moderate	Moderate	High	Low	Moderate
Morita 2012[535]	Low	High	Low	Low	Moderate	Low	Moderate
Sun, 2018[537]	Low	Unclear	Moderate	Moderate	High	Low	Moderate
Studies of periodontal disease and incident diabetes mellitus							
Alshihayb, 2020[532]	Moderate	Low	Low	High	Moderate	Low	High
Demmer, 2008[539]	Low	Low	Moderate	Moderate	Moderate	Low	Moderate
Ide, 2011[540]	Low	Moderate	Low	Low	Moderate	Low	Low
Kebede, 2018[542]	Low	High	Low	Low	Moderate	Low	Low
Lee, 2017[545]	Low	Low	Low	Low	Moderate	Low	Low
Lin, 2014[538]	Low	Unclear	High	Moderate	High	Low	High
Miyawaki, 2016[541]	Low	Moderate	High	Low	Moderate	Low	High
Morita, 2012[535]	Low	High	Low	Low	Moderate	Low	Moderate
Myllymaki, 2018[543]	Moderate	High	Low	Low	Moderate	Low	Moderate
Winning, 2017[544]	Low	Low	Low	Low	Moderate	Low	Low

Table S6: Certainty of evidence by applying the GRADE tool

Certainty assessment							Relative risk (95% CI)	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Periodontal diseases and incidence of diabetes mellitus								
10	observational studies	not serious	serious[a]	serious[b]	not serious	Dose response gradient	**RR 1.26** (1.12 to 1.41)	⨁⨁⨁◯ MODERATE
Diabetes mellitus and incidence of periodontal diseases								
7	observational studies	not serious	not serious[c]	serious[b]	not serious	none	**RR 1.24** (1.13 to 1.37)	⨁⨁⨁◯ MODERATE

[a] RR ranges from 0.78 to 2.91 , and 95% CIs do not overlap; I^2: 71%

[b] different assessment methods were used to diagnose the disease (e.g. defined by self-reports, clinical examinations or a combination of both), some cohorts include participants with type 1 and type 2 diabetes, different time of follow-up

[c] I^2 high (92%), but RRs in same direction

Table S7: Summary relative risks (SRRs) and 95% confidence intervals (95% CIs) of periodontal diseases and incidence of diabetes mellitus by subgroups

	n of studies	SRRs (95% CIs)	I^2 (%)	P_{within}	$P_{between}$
All studies	10	1.26 (1.12, 1.41)	71	<0.0001	
Sex[a]					0.109
Men	5	1.31 (1.01, 1.70)	58	0.048	
Women	2	2.00 (1.58, 2.54)	0	0.974	
Risk of bias					0.127
Low	4	1.09 (0.90, 1.32)	67	0.028	
Moderate	3	1.66 (1.35, 2.03)	10	0.331	
High	3	1.30 (1.04, 1.63)	34	0.219	
Type of diabetes					0.080
Type 1 diabetes	-	-	-	-	
Type 2 diabetes	8	1.41 (1.19, 1.67)	63	0.009	
Type 1 + type 2 diabetes	2	0.98 (0.67, 1.44)	85	0.009	
Assessment of diabetes					0.951
Low risk of bias	7	1.24 (1.03, 1.50)	67	0.005	
Moderate risk of bias	2	1.38 (1.01, 1.89)	89	0.002	
High risk of bias	1	1.33 (0.71, 2.51)	no meta-analysis n=1		
Assessment of periodontal diseases					0.613
Low risk of bias	7	1.19 (0.99, 1.42)	60	0.019	
Moderate risk of bias	1	1.64 (1.35, 1.99)	no meta-analysis n=1		
High risk of bias	2	1.35 (0.96, 1.92)	66	0.086	
Geographical location					0.636
Asia	5	1.19 (1.09, 1.30)	55	0.063	
USA	2	1.61 (1.34, 1.94)	0	0.535	
Europe	3	1.20 (0.72, 1.99)	78	0.012	
Duration of follow-up					0.471
<10 years	5	1.34 (1.09, 1.65)	60	0.043	
≥10 years	5	1.22 (0.96, 1.55)	80	<0.0001	
Number of cases					0.495
Cases <1000	8	1.38 (1.08, 1.77)	73	<0.0001	
Cases ≥1000	2	1.16 (1.13, 1.20)	0	0.564	
By smoking status[b]					0.718
Never	3	1.39 (1.10, 1.76)	7	0.340	
Ever	2	1.28 (1.10, 1.66)	78	0.033	

Adjustment for education					0.865
Yes	4	1.29 (0.83, 1.99)	83	<0.0001	
No	6	1.20 (1.10, 1.31)	49	0.082	
Adjustment for smoking status					0.703
Yes	9	1.31 (1.10, 1.56)	74	<0.0001	
No	1	1.19 (1.10, 1.29)	no meta-analysis n=1		
Adjustment for overweight					0.624
Yes	9	1.32 (1.10, 1.58)	72	<0.0001	
No	1	1.16 (1.12, 1.20)	no meta-analysis n=1		
Adjustment for fruit and vegetable intake					-
Yes	-	-	-	-	
No	10	1.26 (1.12, 1.41)	71	<0.0001	
Adjustment for alcohol intake					0.090
Yes	2	1.98 (1.27, 3.11)	19	0.267	
No	8	1.21 (1.09, 1.35)	70	0.002	
Adjustment for physical activity					0.921
Yes	4	1.33 (0.89, 1.97)	84	<0.0001	
No	6	1.18 (1.10, 1.27)	35	0.117	
Adjustment for number of missing teeth					0.488
Yes	1	1.69 (1.00, 2.85)	no meta-analysis n=1		
No	9	1.24 (1.10, 1.39)	76	<0.0001	

P_{within}, P for heterogeneity within each subgroup; $P_{between}$, P for heterogeneity between subgroups with meta-regression

[a] information available from 5 studies [532, 539-541, 544]

[b] information available from 3 studies [539, 540, 543]

Table S8: Summary relative risks (RRs) and 95% confidence intervals (95% CIs) of diabetes mellitus and incidence of periodontal diseases by subgroups

	n of studies	SRRs (95% CIs)	I^2 (%)	P_{within}	$P_{between}$
All studies	7	1.24 (1.13, 1.37)	92	<0.0001	
Sex[a]					0.447
Men	3	1.35 (1.21, 1.51)	0	0.411	
Women	1	1.57 (1.25, 1.98)	no meta-analysis n=1		
Risk of bias					0.404
Low	1	1.95 (1.22, 3.12)	no meta-analysis n=1		
Moderate	4	1.21 (1.08, 1.34)	95	<0.0001	
High	2	1.29 (1,14; 1.47)	0	0.935	
Type of diabetes					0.306
Type 1 diabetes	1	1.66 (1.41, 1.96)	no meta-analysis n=1		
Type 2 diabetes	4	1.25 (1.01, 1.55)	82	0.001	
Type 1 + type 2 diabetes	2	1.18 (1.17, 1.19)	no meta-analysis n=1		
Assessment of diabetes					0.917
Low risk of bias	2	1.44 (0.88, 2.34)	76	0.043	
Moderate risk of bias	4	1.23 (1.11, 1.37)	96	<0.0001	
High risk of bias	1	1.32 (0.77, 2.26)	no meta-analysis n=1		
Assessment of periodontal diseases					0.911
Low risk of bias	3	1.36 (1.00, 1.86)	56	0.124	
Moderate risk of bias	3	1.22 (1.08, 1.38)	97	<0.0001	
High risk of bias	1	1.29 (1.13, 1.47)	no meta-analysis n=1		
Geographical location					0.957
Asia	5	1.23 (1.11, 1.37)	94	<0.0001	
USA	2	1.29 (1.13, 1.47)	0	0.94	
Duration of follow-up					0.484
<10 years	3	1.18 (0.97, 1.43)	78	0.011	
≥10 years	4	1.34 (1.13, 1.58)	84	<0.0001	
Number of cases[b]					0.201
Cases <1000	2	1.63 (1.39, 1.91)	0	0.425	
Cases ≥1000	4	1.21 (1.03, 1.42)	83	<0.0001	
By smoking status[c]					-
Never	1	1.32 (1.06, 1.64)	no meta-analysis n=1		
Ever	1	1.30 (1.14, 1.49)	no meta-analysis n=1		
Adjustment for education					0.272

Yes	2	1.64 (1.12, 2.40)	13	0.285	
No	5	1.22 (1.11, 1.34)	94	<0.0001	
Adjustment for smoking status					0.706
Yes	4	1.28 (1.12, 1.47)	32	0.211	
No	3	1.22 (1.08, 1.38)	97	<0.0001	
Adjustment for overweight					0.746
Yes	3	1.24 (1.12, 1.36)	0	0.611	
No	4	1.25 (1.11, 1.42)	96	<0.0001	
Adjustment for fruit and vegetable intake					0.417
Yes	2	1.49 (1.01, 2.18)	64	0.098	
No	5	1.21 (1.09, 1.34)	94	<0.0001	
Adjustment for alcohol intake					0.417
Yes	2	1.49 (1.01, 2.18)	64	0.098	
No	5	1.21 (1.09, 1.34)	94	<0.0001	
Adjustment for physical activity					0.417
Yes	2	1.49 (1.01, 2.18)	64	0.098	
No	5	1.21 (1.09, 1.34)	94	<0.0001	
Adjustment for number of missing teeth at baseline					0.994
Yes	1	1.29 (1.13, 1.47)	no meta-analysis n=1		
No	6	1.24 (1.11, 1.37)	93	<0.0001	

P_{within}, P for heterogeneity within each subgroup; $P_{between}$, P for heterogeneity between subgroups with meta-regression

[a] information available from 3 studies[532], [534], [537]

[b] information available from 6 studies: one study did not provide number of cases in the text [536]

[c] information available from 1 study [534]

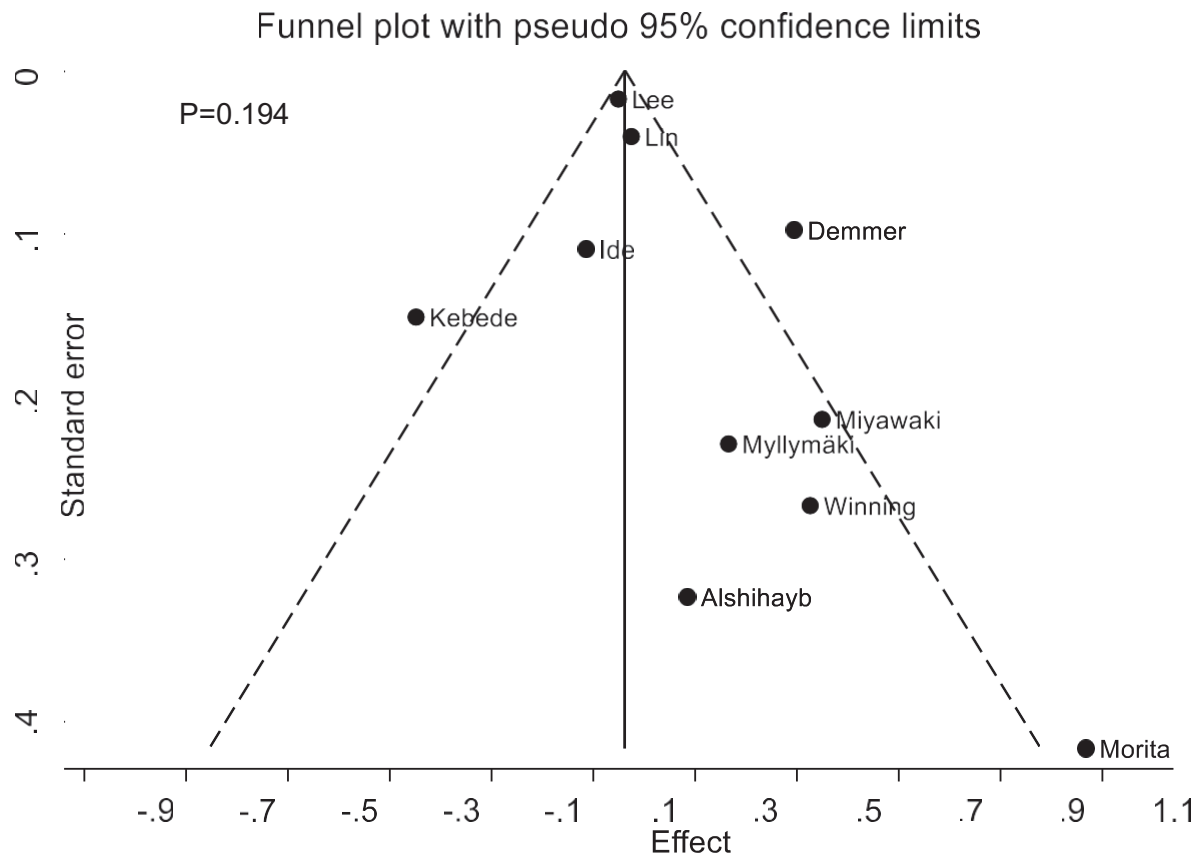

Figure S2. Funnel plot for association between periodontal disease and incidence of diabetes mellitus

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