Research Square

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Epidemiologic relationship between periodontitis and type 2 diabetes mellitus

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Research article

Keywords: Diabetes mellitus, type 2, Periodontitis, Systematic review, Meta-analysis, Epidemiologic Studies

Posted Date: May 28th, 2019

DOI: https://doi.org/10.21203/rs.2.9843/v1

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Version of Record: A version of this preprint was published on July 11th, 2020. See the published version at https://doi.org/10.1186/s12903-020-01180-w.

Abstract

Objectives To systematically reviewing the epidemiologic relationship between periodontitis (PD) and type 2 diabetes mellitus (T2DM). Materials and Methods Four electronic databases were searched up to December, 2018. Manual search including the reference lists of included studies and relevant journals. Observational studies evaluating the relationship between T2DM and PD were included. Meta-analyses were applied using STATA. Results A total of 53 observational studies were included. Pooled results of cross-sectional studies found the strength of association between these two diseases was very strong (OR=3.27, p=0.000). Adjusted T2DM prevalence was significantly higher in PD patients (OR=4.04, p=0.000) and vice versa (OR=1.58, p=0.000). T2DM patients had significantly worse periodontal status, reflected in a 0.61mm deeper periodontal pocket, a 0.89mm higher attachment loss and about 2 more lost teeth (all p=0.000). Results of cohort studies found T2DM could elevate 27% risk of developing PD (p=0.000). Glycemic control state of T2DM might result in different PD outcomes. Severe PD increased 53% of incident T2DM (p=0.000) and this result was stable. In contrast, the impact of mild PD on T2DM incidence (RR=1.28, p=0.007) was less robust. Conclusions There is an evident bidirectional relationship between T2DM and periodontitis. Further well-designed cohort studies are needed to confirm this. Clinical Relevance Both dentists and physicians need to be aware of this strong connection between PD and T2DM. Control these two diseases might benefit the prevention of the incidence of each other.

Introduction

Diabetes mellitus (DM) is a common metabolism disease results from a defect in insulin secretion, a defect in insulin action or a combination of both [1]. Type 2 DM (T2DM) results from the body's ineffective use of insulin comprises the 90% of people with DM worldwide [2]. The number of people with DM has risen more rapidly in the decades from 108 million in 1980 to 422 million in 2014, and the number is likely to be more than double in the next 20 years. Furthermore, WHO projected that diabetes will be the seventh leading cause of death in 2030 [3].

Periodontitis (PD) is a chronic, multifactorial inflammatory disease in the underlying supporting tissues surrounding teeth. Sufferers may result in gingivitis, loss of periodontal attachment, resorption of alveolar bone, and eventually loss of tooth [4]. Severe PD, which is the sixth most prevalent chronic disease among general population, affects nearly 750 million people worldwide and is blamed on affecting people's chewing ability, nutritional status and quality of life [5,6].

T2DM and PD have a bidirectional relationship which is well documented in quantities of reviews and epidemiological studies [7-9]. PD is defined as the sixth complication of DM, which means DM can promote the progression of PD [10]. Conversely, PD is now known as a risk factor for worsening glycemic control and may increase the risk for diabetic complications [11]. Mechanically, T2DM influences PD initial and progression by causing hyper-inflammatory response, impaired bone repair, and advanced glycation end products [9,12,13]. PD as a local focus of infection can cause the level of IL-6, TNF-a, and CRP increasing in systems, resulting in increased systemic inflammation which contributes to insulin

resistance [14]. Based on the biological hypothesis, there are substantial randomized controlled trails (RCTs) found periodontal treatment can improve glycemic control [15]. However, two well-designed large scaled RCTs obtained contradictory results on whether periodontal treatment had effect on glycated hemoglobin (HbA1c) for T2DM patients [16,17].

The above contradiction raised our curiosity. Do these two common diseases really affected each other? However, after systematically literature searching, we found so far there is no systemic review that answers this question comprehensively. In the present work, we summarized evidence from observational studies to explore this bidirectional relationship.

Materials And Methods

The protocol of the present systematic review was registered in PROSPERO (CRD42018089993). All procedures were done following this protocol and in accordance with the MOOSE statements [18]. Two authors independently achieved study selection, quality assessment and data extraction. Any controversies were solved by consensus discussion.

Search strategy

The searching strategy was a combination of electronic search and manual search. Manual search including the reference lists of included studies and the following journals: Diabetes care, Journal of Periodontology, Journal of Clinical Periodontology and Journal of Dental Research. The following electronic data bases were searched without language limitation: MEDLINE (OVID, 1948 to December 2018), EMBASE (OVID, 1984 to December 2018), Chinese BioMedical Literature Database (CBM, 1978 to December 2018), and China National Knowledge Infrastructure (CNKI, 1994 to December 2018). MeSH terms with free text words were combined when conducting electronically search. The MeSH terms used for PD were “Periodontal Diseases” and “Periodontitis”. The free text word was “(periodont$ or gingivitis or gingiva$ or gum$).mp.”. The MeSH term used for T2DM searching was “Diabetes Mellitus, Type 2”. Free text words were “(((non-insulin or noninsulin or type 2 or type II or matur$ or adult) adj4 (DM or diabet$)) or T2DM or DMT2 or NIDDM or MODY).mp.”. The titles and abstracts were initially scanned, and the full texts of the possibly eligible studies were obtained for final judgment.

Inclusion criteria

Observational studies (cross-sectional studies, case-control studies and cohort studies) investigating the relationship between T2DM and PD were included. The outcomes for PD were required to be clinical attachment loss (CAL), periodontal pocket depth (PPD), number of teeth (NOT), loss of teeth (LOT) and so forth. The outcomes for T2DM were required to be oral glucose tolerance test (OGTT), HbA1c and fasting plasma glucose (FBG). Disease (PD or T2DM) prevalence and incidence were also included. The participants were required to represent the natural population grouping into PD versus non-PD, or T2DM

versus non-DM. Comparisons based on PD parameters, such as comparing the T2DM incidence/prevalence between patients with low CAL level and high CAL level, were also included. Studies investigating outcomes in selected population, such as co-morbidity patients, all PD patients, all T2DM patients or all healthy participants (PD-free and T2DM-free), would be excluded. Exposures should be selected according to the aforementioned PD/T2DM related parameters, medical records or self-reported medical history.

Methodological quality assessment

Study quality of cohort studies and case-control studies were measured by Newcastle-Ottawa Scale (NOS) scoring system. Studies with score less than 3 were regarded as low quality and would be excluded. For cross-sectional studies, the Agency for Healthcare Research and Quality (AHRQ) scoring system was applied. Studies with score less than 3 in AHRQ scoring system were regarded as low quality and would not be included.

Data extraction

The extracted data was as follows: 1) investigator, 2) country, 3) number of participants, 4) age and sex of participants, 5) recruitment of participants, 6) selected outcomes, and 7) NOS/AHRQ score. For cohort studies, the follow up period and number of incident cases were also extracted.

Data analysis

The software STATA 14.0 was utilized for meta-analysis. Weighted mean differences (WMD) with 95% confidence interval (CI) were calculated for continuous data. Odds ratio (OR), risk ratios (RR) with 95% CI were calculated for dichotomous data. Generic inverse variance (lnOR or lnRR) was applied for meta-analyses included studies only reported OR or RR. The significance was determined by two sides α value with a cut-off p value of 0.05. Meta-analyses were done under the random-effects model if included more than 4 studies (≥5); otherwise, the fixed model would be applied. Cochran's Q test and I^2 static were used for detecting statistical heterogeneity among studies. When P>0.10 and I^2<50%, it was regarded as low heterogeneity; otherwise, it was regarded as high heterogeneity. The meta-regression was applied for a meta-analysis included more than 4 studies to investigate possible sources of heterogeneity. The influence test was applied by deleting every single study in turn to test whether the results were stable. For a meta-analysis included more than 10 studies, the publication bias was detected by Egger's test and Begg's test. It would be regarded as no publication exist when both test results found p>0.05. If publication bias existed or unstable results were found, the trim and fill method would be applied.

Results

Results of search and characteristics of included studies

A total of 1387 studies were identified from primary search after removal of duplication. After screening the titles and abstracts, 73 studies were identified for further evaluation. After full text browsing, 50 studies were considered eligible for inclusion, and 23 studies were excluded with reasons. Additional reference checking obtained 3 included studies. Journal searching did not add any new studies. Finally, a total of 53 studies were included in the present work. Figure 1 showed the searching and including process. Appendix Table S1 and S2 summarized the characteristics of 43 [19-61] cross-sectional studies and 12 [62,23,63-68,39,69-71] cohort studies, respectively. All included cross-sectional studies and cohort studies were scored more than 3.

After systematically reviewing the included studies, we found included studies answered 3 questions (question 1-3, Q1-3). Specifically, cross-sectional studies gave the answer of “Q1: Are PD and T2DM associated with each other?” Cohort studies gave the answer of the other two questions: “Q2: Does T2DM increase risk of developing PD?”, and “Q3: Does PD increase risk of developing T2DM?”

Results of meta-analyses

Q1: Are PD and T2DM associated with each other?

A total of 43 cross-sectional studies were included to answer Q1. Evidences were from some national large-scale population-based studies, such as SHIP, NHANES and KCIS, and some small-sample studies recruiting participants from communities or hospitals. Among these studies, only 14 studies reported adjusted outcomes (table 1). Seven meta-analyses were applied as follows.

Strength of association between PD and T2DM

For evaluating the strength of association between PD and T2DM, we extracted data of cross-sectional studies for 2 × 2 contingency table ((T2DM, PD), (T2DM, No PD), (No T2DM, PD) and (No T2DM, No PD)). A total of 15 cross-sectional studies with 17924 participants were included into meta-analysis. After pooling the original data, we found the strength of this association was very strong (OR=3.27, 95%CI 2.36-4.51, p=0.000, figure 2a). Since the original data was not directional adjusted, this obvious association could be explained as PD prevalence was significantly higher in T2DM patients, or it could also be summarized as T2DM prevalence was significantly higher in PD patients. Influence analysis demonstrated that the pooled result was stable (figure S1a). No publication bias was detected (egger, p=0.792; begg, p=1.000). Significant heterogeneity was detected (p=0.000; I^2=86.3%).

Directional adjusted T2DM prevalence (PD versus non-PD)

A total of 6 cross-sectional studies were included and all took T2DM prevalence as outcome. 3 studies with 1956 participants were included into a meta-analysis which selected diagnosed PD as exposure. Included studies had no significant heterogeneity. The result showed that PD patients had significantly higher odds in T2DM prevalence compared to participants with no PD (OR=4.04, 95%CI 2.48-6.59, p=0.000, figure 2b). Influence analysis showed the pooled result was stable (figure S1b). Other exposures including CAL, PPD, LOT, tooth mobility and alveolar bone loss. The results all proved T2DM was more prevalent in participants with worse periodontal health (table 1).

Directional adjusted PD prevalence (T2DM versus non-DM)

A total of 8 cross-sectional studies were included and all took T2DM as exposure. Three studies with 11459 participants were included into a meta-analysis evaluating PD prevalence. No significant heterogeneity was detected. The result showed that T2DM patients had significantly higher OR in PD prevalence (OR=1.58, 95%CI 1.38-1.81, p=0.000, figure 2c). Influence analysis indicated that the pooled result was stable (figure S1c). Besides PD prevalence, other outcomes were divergent. In brief, all studies demonstrated the PD related parameters were more prevalent in T2DM patients, though some of the differences were not statistically significant. The results were summarized in table 1.

CAL level differences between T2DM and DM free participants

18 cross-sectional studies with 9571 participants were included. Significant heterogeneity was detected (p=0.000; I^2=92.5%). Pooled result showed the T2DM patients had a 0.89 mm higher CAL than controls (WMD=0.89, 95%CI 0.64-1.15, p=0.000, figure 2d). Influence analysis demonstrated that the pooled result was stable (figure S1d). Publication bias was detected by Egger's and Begg's test (egger, p=0.003; begg, p=0.015). Then we applied trim and fill method to further evaluate the publication bias and found that the results were still significantly positive after adding hypothesized studies (table S3).

PPD differences between T2DM and DM free participants

17 cross-sectional studies with 8982 participants were included. Significant heterogeneity was detected (P=0.000; I^2=94.5%). Pooled result showed the periodontal pockets of T2DM patients were 0.61 mm deeper than controls (WMD=0.61, 95%CI 0.42-0.79, p=0.000, figure 2e). Influence analysis demonstrated that the pooled result was stable (figure S1e). Publication bias was detected by Egger's and Begg's test

(egger, p=0.015; begg, p=0.006). However, adding hypothesized studies by trim and fill method still resulted in strong significance (table S3).

NOT differences between T2DM and DM free participants

9 cross-sectional studies with 4415 participants were included. Significant heterogeneity was detected (p=0.000; I^2=86.6%). Pooled result showed the T2DM patients had on average 2.01 fewer teeth remained than controls. (WMD=-2.01, 95%CI -3.20–0.82, p=0.000, figure 2f). Influence analysis demonstrated that the pooled result was stable (figure S1f). No publication bias was detected (egger, p=0.723; begg, p=0.917).

LOT differences between T2DM and DM free participants

11 cross-sectional studies with 3405 participants were included. Significant heterogeneity was detected (P=0.000; I^2=90.7%). Pooled result showed the T2DM patients had on average 2.22 more tooth lost than controls. (MD=2.22, 95%CI 0.94-3.49, p=0.000, figure 2g). Influence analysis demonstrated that the pooled result was stable (figure S1g). No publication bias was detected (egger, p=0.230; begg, p=0.755).

Meta-regression for meta-analyses with huge heterogeneity

Huge statistic heterogeneity existed in the above 5 meta-analyses, the I^2 ranged from 86.3% to 94.5%, thus we did meta-regression to find the possible sources of heterogeneity. The available covariates included number of participants, mean age, major gender composition, geographic area and AHRQ scores. However, single variable regression did not find any significant covariates; multiple-regression of these covariates only explained about 10% heterogeneity of all meta-analyses (data not shown). The significant heterogeneity might be caused by excessive number of included studies and related statistical heterogeneity.

Q2: Does T2DM increase risk of developing PD?

A total of 6 cohort studies were considered eligible. The results were summarized in table 2. Two meta-analyses on PD incidence were done as follows. Due to the limited included study number, fixed model

was applied in this section. Besides PD incidence, other outcomes, including LOT, PPD, CAL and alveolar bone loss, were also reported. The results were summarized in table 2.

Four studies which investigating whether manifest T2DM increase PD incidence were included into one meta-analysis. In total, 46191 participants including 2548 T2DM patients were included, with a follow-up period range from 2.6 to 20 years. A total of 6361 incident PD were detected. The result showed that T2DM led to a 27% elevated risk for incident PD (RR= 1.27, 95%CI 1.15-1.40, p=0.000, figure 3a). A slight heterogeneity among studies was detected (I^2=54.7%, p=0.085). Influence analysis found this result was stable (figure S2a).

Another meta-analysis was carried out for investigating the impact of well-controlled and poorly-controlled T2DM for PD incidence. In total, two studies with 2791 participants were included. 94 well-controlled and 89 poorly-controlled T2DM at baseline was selected as exposure group. The follow-up was 2.3 (1.2-6.9) and 5 years, respectively. Pooled results of these two studies found well-controlled T2DM did not increase the risk of tooth loss or alveolar bone absorption (RR= 1.05, 95%CI 0.83-1.32, p=0.709, figure 3b); In contrast, poorly controlled T2DM significantly promoted the incidence of tooth loss and alveolar bone absorption (RR= 1.41, 95%CI 1.15-1.73, p=0.001, figure 3b).

Q3: Does PD increase risk of developing T2DM?

A total of 7 cohort studies were included. The results were summarized in table 3. In total, 27498 participants were included. Among these participants, 8701 had mild PD, while 3994 had severe PD. A total of 1772 incident T2DM were detected during a follow-up period ranged from 5 to 18 years. Interestingly, all the included studies reported their results based on PD severity. Thus, we did two meta-analyses according to the PD severity as follows.

The impact of mild periodontitis on T2DM incidence

Meta-analysis on this topic showed that mild PD led to a 28% elevated risk for incident PD (RR= 1.28, 95%CI 1.07-1.54, p=0.007, figure 4a). No significant heterogeneity (I^2=20.4%, p=0.27) or publication bias (egger, p=0.133; begg, p=0.133) among studies were detected. Influence analysis found this result was unstable (Figure S2b). Deleting Demmer's study [63] would reduce the effect size and obtain a marginally significant result (RR=1.17, 95%CI 0.99-1.39, p>0.05). Due to this unstable result, we applied trim and fill method. After adding 3 hypothetical studies, the results changed into significant (RR=1.14, 95%CI 0.92-1.41, p=0.23, table S3). The above results indicating that the effect of mild PD on T2DM incidence was not very robust.

The impact of severe periodontitis on T2DM incidence

Pooled results showed that severe PD increased 53% risk of T2DM incidence (RR= 1.53, 95%CI 1.27-1.83, p=0.000, figure 4b). The heterogeneity was very low (I^2=0%, p=0.649). No publication bias (egger, p=0.104; begg, p=0.230) were detected. In contrast to mild PD, influence analysis found the impact of sever PD was very stable (figure S2c). To further confirm this, we applied trim and fill method. After adding 2 hypothetical studies, the results were still significant (RR=1.46, 95%CI 1.23-1.73, p=0.000, table S3). The above results indicated the effect of severe PD on T2DM incidence was solid.

Discussion

In this systematic review, we summarized the observational studies exploring the bidirectional relationship between PD and T2DM. Cross-sectional studies supported that there was a strong connection between PD and T2DM. Prospective studies supported that T2DM and PD promoted the incidence of each other in a dose-dependent way.

The strength of our work mainly lied on including the most up-to-date evidence and analyzing sufficient studies and participants. However, limitations of our work were also worth noting.

For cross-sectional studies (Q1), huge statistic heterogeneity existed among studies in 5 of our 7 meta-analyses. However, we did not find the significant covariates which could decrease the heterogeneity. Several reasons could partially explain the heterogeneity. Firstly, these meta-analyses included large quantities of studies which would inevitably result in a significant statistic diversity and cause statistical heterogeneity. Secondly, heterogeneity may result from measurement diversity. For example, the definitions of PD were distinct, which could be based on a CPI code or clinical signs and symptoms. For CAL and PPD, measurement diversity was from the selection of tooth and probing sites. Thirdly, the unreported confounding factors also caused heterogeneity. In contrast with the 2 meta-analyses with limited heterogeneity based on adjusted OR, the other 5 meta-analyses with huge heterogeneity were all based on crude data. Little of the included studies reported the confounding factors. This might partially explain why our meta-regression was an attempt of futility.

For cohort studies, we summarized that T2DM and PD promoted the incidence of each other in a dose-dependent way. Even though “a dose-dependent way” seemed to be a very attractive conclusion, it actually was not that solid. This conclusion was drawn from subgroup analysis of limited studies. To further confirm this, the generalized least-squares trend estimation[72,73] or meta-regression should be applied. However, due to the inconsistency of exposure/outcome selection among limited studies, these analyses could not be taken. It is also worth noting the dose-dependent phenomenon also presented in the adjusted results of cross-sectional studies (table 1) in certain degree.

Several important works not included in our study were worth reading. Chiu's study[62] and Joshipura's study[74] found PD could increase the risk of developing pre-diabetes. Demmer's study[75] found PD was associated with 5-year HbA1c progression. Also, in the present work we did not include studies focusing other aspects of the connection between PD and T2DM. Very recently, the joint workshop between European Federation of Periodontology and International Diabetes Federation updated a systematic review on the effect of PD on diabetes.[76] In this systematic review, they concluded for T2DM patients, PD is associated with higher levels of HbA1c and significantly worse diabetes-related complications. This article makes up the deficiency of our work in some degree and the details are definitely worth reading.

For future studies, several considerations on study design should pay attention. In our included studies, some researchers[21,30,34,37] defined their studies as case-control studies by mistake. The control group was age and sex matched with the cases; however, the cases (T2DM patients) were not newly diagnosed but were diagnosed for years. Both T2DM and PD are all chronic diseases which cannot be cure once onset, they might aggravate each other in a positive feed-back way. Thus, once selected participants suffered from T2DM for years, it would become a puzzle since their worsened periodontal health could be regarded as the cause of T2DM as well as the effect of T2DM. Therefore, the study design of these studies should not be regarded as case-control; actually, it was case-matched cross-sectional design, since it could not distinguish the onset time of T2DM or PD. This also applied for cohort studies. Incident

outcome, especially T2DM, reported within 1 year of baseline should be excluded for minimizing the prevalence of undiagnosed baseline T2DM.[63,71] This also indicating the longer follow-up period of cohort studies investigating these two diseases are required.

Seen from the included studies with adjusted results, significant confounding factors in this bidirectional relationship included age, gender, body mass index, waist, C-reactive protein, white blood cell count, hypertension, triglyceride, smoking status, education, income, frequency of dentist visits and so forth. For deepening the knowledge of this bidirectional relationship between PD and T2DM, we suggested that the future observation studies should take these confounding factors into consideration. For researchers, these confounders should be recorded, described and analyzed detailly. Besides, there was a trend that this bi-directional relationship might be dose-dependent. Future studies could pay more attention and applying subgroup or regression analysis.

Declarations

Compliance with Ethical Standards

Conflict of Interest: All authors declare that they have no conflict of interest.

Funding: The work was supported by National Nature Science Foundation of China (81472532), Key Technology R&D Program of Sichuan Province of China (2016SZ0063), and Graduate Student's Research and Innovation Fund of Sichuan University (2018YJSY106).

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: For this type of study, formal consent is not required.

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Tables

Table 1 Summary of adjusted results of cross-sectional studies

Study	Evaluated PD related conditions	Definition of T2DM	Main conclusion and outcome
		PD/non-PD	
Awuti 2012[20]	Moderate PD: PPD ≤6 mm, or CAL of 3-4 mm; or possible presence of slight loose teeth (N=98) Severe PD: PPD >6 mm, or CAL ≥5 mm; or more than one loose tooth (N=77) Control: non-PD (N=509)	The 1999 WHO criteria and ADA standards	T2DM was more prevalent in moderate PD compared with no PD. Adjusted OR=4.033, 95%CI 2.069-7.861 T2DM was more prevalent in severe PD compared with no PD. Adjusted OR=2.313, 95%CI 1.042-5.137
Choi 2011[22]	Top quintile category versus the bottom quintile CAL: Quintile 1 mean CAL=0.2mm (N=2412) Quintile 5 mean CAL=3.0mm (N=2453)	ADA criteria	T2DM was more prevalent in mean CAL 3.0mm compared with mean CAL 0.2mm. Adjusted OR=4.77, 95%CI 2.69–8.46
	Top quintile category versus the bottom quintile PPD: Quintile 1 mean PPD=0.7mm (N=2451) Quintile 5 mean PPD=2.2mm (N=2449)		T2DM was more prevalent in mean PPD 2.2mm compared with mean PPD 0.7mm. Adjusted OR=1.63, 95%CI 1.10–2.42
Mohamed 2013[37]	Chronic PD: at least one site with PPD of >4mm (N=290) Control: non-PD (N=157)	The 1999 WHO criteria	T2DM was more prevalent in chronic PD compared with non-PD. Adjusted OR=4.07, 95%CI 1.74–9.49
	Tooth mobility (N=153)		T2DM was more prevalent in participants with tooth mobility compared with those without.

	Control: without tooth mobility (N=294)		Adjusted OR=5.90, 95%CI 2.26–15.39
	NOT >21 teeth (N=381) Control: NOT≤21 teeth (N=66)		T2DM was less prevalent in participants with >21teeth, with an OR of 0.23. Adjusted OR=0.23, 95%CI 0.08–0.63
Nesse 2010[40]	PD: CPITN score was ≥3, indicating PPD ≥4 mm (N=217) Control□non-PD (N=320)	Clinical examination; or medical record	T2DM was more prevalent in PD compared with non-PD. Adjusted OR=4, 95%CI 1.03-15.3
Saito 2004[46]	high portion category compared in the low portion CAL: Low mean CAL< 1.5mm (N=18) High mean CAL>2.5mm (N=38)	The WHO criteria	T2DM was more prevalent in mean CAL >2.5mm compared with mean CAL 0.2mm. Adjusted OR=2.0, 95%CI 1.0-3.9
	PPD: Low mean PPD<1.3mm (N=18) High mean PPD>2.0mm (N=32)		T2DM was more prevalent in mean PPD >2.0mm compared with <1.3mm. Adjusted OR=2.6, 95%CI 1.3-5.0
Saito 2006[45]	Mean alveolar bone loss (N=131) Control: Low alveolar bone loss (N=49)	The WHO criteria	Mean alveolar bone loss as a continuous variable showed a 1% increase in mean alveolar bone loss corresponded to a 6% increased prevalence of T2DM. Adjusted OR=1.06 95%CI 1.00-1.12
		T2DM/non-T2DM	
Kaur 2009[25]	Top quartile compared with three lower quartiles LOT (Quartile 4 vs 1-3)	T2DM: After the age of 29; or insulin started >1 year after disease onset (N=310) Non-T2DM (N= 1858)	The OR for increase tooth loss was 1.65 times higher for the T2DM patients compared with non-T2DM participants. Adjusted OR=1.65, 95%CI 1.13–2.39
Kowall	PD: at least 2 non-	Poorly controlled	PD was more prevalent in poorly controlled T2DM

2015[27]	adjacent teeth CAL≥3mm	T2DM HbA1c ≥7% (N=64) Better controlled T2DM HbA1c<7% (N=137) Non-T2DM (N=2145)	patients compared with non-T2DM participants, which was not statistically significant. Adjusted OR=1.60 95%CI 0.55-4.63 The prevalence of PD showed no difference between better controlled T2DM patients and non-T2DM participants. Adjusted OR=0.94 95%CI 0.52-1.67
	Top quartile compared with three lower quartiles Mean CAL ≥ 4mm (Quartile 4 vs 1-3)		The OR for CAL≥4mm was 1.36 times higher in poorly controlled T2DM patients compared with non-T2DM participants, which was not statistically significant. Adjusted OR=1.36 95%CI 0.75-2.49 The prevalence of CAL≥4mm showed no difference between better controlled T2DM patients and non-T2DM participants. Adjusted OR=0.94 95%CI 0.61-1.45
	Top quartile compared with three lower quartiles Mean PPD (Quartile 4 vs 1-3)		The OR for top PPD was 1.31 times higher for the poorly controlled T2DM patients compared with non-T2DM participants, which was not statistically significant. Adjusted OR=1.31 95%CI 0.75-2.30 The prevalence of mean PPD showed no difference between better controlled T2DM patients and non-T2DM participants. Adjusted OR=1.13 95%CI 0.75-1.71
	Lowest quartile compared with three higher quartiles NOT (Quartile1 vs 2-4)		The OR for NOT was 1.49 times higher in poorly controlled T2DM patients compared with non-T2DM participants, which was no statistically significant Adjusted OR=1.49 95%CI 0.92-2.40 NOT showed no difference between better controlled T2DM patients and non-T2DM participants. Adjusted OR=1.05 95%CI 0.74-1.50
Leung 2008[30]	Chronic PD: CPI score of 4 in any one sextant (WHO, 1997).	T2DM: Clinical examination; or medical record (N=364) Non-T2DM (N=161)	PD was more prevalent in T2DM patients compared with non-T2DM participants. Adjusted OR= 1.84 95%CI 1.22-2.77
	CAL≥ 6 mm		The OR for CAL ≥ 6 mm was 1.71 times higher for T2DM patients compared with non-T2DM participants. Adjusted OR=1.71, 95%CI 1.13-2.59

Nelson 1990[39]	PD: <24 teeth present;> 6 teeth with ≥25% bone loss and any tooth with ≥50% bone loss.	T2DM: OGTT ≥11.1mmol/l (N=720) Non-T2DM (N=1553)	PD was more prevalent in T2DM patients compared with non-T2DM patients. Adjusted OR=1.64, 95%CI 1.50-1.79
Saito 2005[47]	Mean PPD ≥1.9mm	T2DM: The WHO criteria (N=27) Non-T2DM (N=360)	The OR for PPD≥1.9mm was 1.4 times higher for the T2DM patients compared with non-T2DM participants, which was not statistically significant. Adjusted OR=1.4 95%CI 0.6-3.2
	Mean CAL ≥2.42mm		The OR for CAL≥2.42mm was 1.5 times higher for the T2DM patients compared with non-T2DM participants, which was not statistically significant. Adjusted OR=1.5 95%CI 0.7-3.2
Tanwir 2009[51]	Missing fewer teeth	T2DM: Clinical examination; or medical record (N=88) Non-T2DM (N=80)	The OR for missing or fewer teeth was 2.3 times higher for the diabetic patients compared with non-T2DM patients. Adjusted OR=2.3 95%CI 1.32-4.14
Tsai 2002[52]	Severe PD: at least two sites CAL ≥6mm at least one site PPD ≥5mm	Poorly control T2DM，HbA1c ≥9% (N=170) Better control T2DM，HbA1c<9% (N=260) Non-T2DM (N=3841)	Severe PD was more prevalent in poorly controlled T2DM patients compared with non-T2DM participants. Adjusted OR=2.90 95%CI 1.40-6.03 Severe PD was more prevalent in better controlled T2DM patients compared with non-T2DM participants, but was not statistically significant. Adjusted OR=1.56 95%CI 0.90-2.68
Wang 2009[53]	PD: The WHO 1997 criteria	T2DM: The 1999 WHO criteria (N=193) Non-T2DM (N=8468)	PD was more prevalent in T2DM patients compared with non-T2DM participants. Adjusted OR=1.34 95%CI 1.07-1.74

PD: periodontitis; T2DM: type 2 diabetes mellitus; CAL: clinical attachment loss; PPD: periodontal pocket depth; NOT: number of teeth; LOT: loss of teeth; HbA1c: glycated haemoglobin; OR: odds ratio; CPI: community periodontal index; RPI: Russell periodontal index.

Table 2 Summary of results of cohort studies

Study	Characteristics	Definition of outcome	Definition of exposure	Main conclusion and outcome
T2DM/non-T2DM				
Chiu 2015[62]	Taiwan, KCIS study 5y FU (2003-2008)	Binary variable PD: CPI≥3 Non-PD: CPI<3	T2DM: FBG≥126mg/dl or self-reported T2DM (N=57) Pre-diabetes: 100≤FBG<126 mg/dl (N=297) None: FBG<100mg/dl (N=4033)	T2DM led to a 95% elevated risk for incident PD. Adjusted HR=1.95, 95%CI 1.22–3.13 Pre-diabetes led to a 25% elevated risk for incident PD. Adjusted HR=1.25, 95%CI 1.00–1.57
Demmer 2012[23]	Germany, SHIP study 5y FU (1997-2006)	Binary variable Tooth loss or not	T2DM: Self-reported age>30 years old, or HbA1c≥6.5%, timing of insulin therapy initiation >1 year from diagnosis Controlled T2DM: HbA1c≤7% (N=80) Uncontrolled T2DM: HbA1c>7% (N=72) Control: no DM (N=2280)	Controlled T2DM did not lead to an elevated risk for tooth loss. Adjusted RR=1.01, 95%CI 0.79–1.28 Uncontrolled T2DM led to a 36% elevated risk for tooth loss. Adjusted RR=1.36, 95%CI 1.11–1.67
		Continuous variable Mean PPD change; Mean CAL change;		Controlled T2DM did not lead to an increased PPD and CAL change. Adjusted MD=0.04 and 0.09 mm, p>0.05 Uncontrolled T2DM led to a significant increase in PPD and CAL change. Adjusted MD=0.18 and 0.37 mm, p<0.05
Jimenez 2012[65]	USA, HPFS study, 20y FU (1986-NA)	Binary variable PD: self-reported; Tooth loss: self-reported	T2DM: self-reported T2DM (N=2285) Control: non-T2DM (N=32962)	T2DM led to a 29% elevated risk for incident PD. Adjusted RR=1.29, 95%CI 1.13–1.47 T2DM led to a 9% elevated risk for incident tooth loss. Adjusted RR=1.09, 95%CI 1.01–1.18

Morita 2012[68]	Japan, 5y FU (1997-2006)	Binary variable PD: CPI≥3 Non-PD: CPI<3	T2DM: HbA1c≥6.5% (N=150) Control: HbA1c<6.5% (N=5706)	T2DM led to a 17% elevated risk for incident PD. Adjusted RR=1.17, 95%CI 1.01–1.36
Nelson 1990[39]	USA, Pima Indians study, Mean 2.6y FU (1983-1989)	Binary variable PD: <24 teeth present;> 6 teeth with ≥25% bone loss and any tooth with ≥50% bone loss. Non-PD: ≥24 teeth present; <6 could have 25-50% bone loss and the rest <25% bone loss	T2DM: OGTT ≥ 11.1mM(N=56) Control: no T2DM (N=645)	T2DM led to a 160% elevated risk for incident PD. Adjusted RR=2.57, 95%CI 1.0-6.6, p<0.05
Taylor 1998[69]	USA, Pima Indians study, Mean 2.3y FU (1.2-6.9 years)	Mean alveolar bone loss bone scores corresponded to bone loss of 0%, 1%to 24%, 25% to 49%, 50% to 74%, or > 75%	Diagnosed by OGTT (>200mg/dl) Better controlled T2DM: HbA1c≥9% (N=7) Poorer controlled T2DM: HbA1c<9% (N=14) Control: no T2DM (N=338)	Better controlled T2DM led to a 120% elevated risk for alveolar bone loss progression, but was not statistically significant. Adjusted OR=2.2, 95%CI 0.7–6.5, p=0.175 Poorer controlled T2DM led to a 1040% elevated risk for alveolar bone loss progression. Adjusted OR=11.4, 95%CI 2.5–53.3
			PD/non-PD	
Demmer 2008[63]	USA, NHEFS study	T2DM: Death certificate; self-	Category of baseline periodontal index, control group was	Compared to the control group, participants in the 1st or 2nd categories did not experience an increased OR of developing T2DM,

	17y FU (1971-1992)	reported T2DM and received anti-diabetes medications; facility discharge diagnosis	the participants with lowest RPI score	whereas the odds increased sharply in the 3rd category (OR 2.08; P< 0.0001). The ORs in 4th (1.71; P=0.003) and 5th (1.50; P=0.06) categories abated but remained elevated and were not statistically significantly different from the odds for those in the 3rd category.
			PD: clinical diagnosed(N=1662)	PD led to a 50% elevated risk for incident T2DM.
			Gingivitis: clinical diagnosed (N=2135) Control: periodontium health (N=3372)	Adjusted OR≈1.50, 95%CI NA, p<0.05 Gingivitis led to a 40 % elevated risk for incident T2DM. Adjusted OR≈1.40, 95%CI NA, p<0.05
			Exposure: LOT 25-31 (N=NA) Control: LOT 0-8 (N=NA)	Loss more teeth at baseline led to a 70% elevated risk for incident T2DM. Adjusted OR≈1.70, 95%CI NA, p<0.05
Ide 2010[64]	Japan, 6.3y FU (2000-2007)	T2DM: FBG≥125mg/dl	Exposure1: CPI=4 (N=490) Exposure2: CPI=3 (N=2167) Control: CPI<3 (N=3191)	CPI=4 led to a 28% elevated risk for incident T2DM, but was not statistically significant. Adjusted HR=1.28, 95%CI 0.89–1.86 CPI=3 did not led to an elevated risk for incident T2DM. Adjusted HR=1.00, 95%CI 0.77–1.30
			Exposure1: LOT>3 (N=748) Exposure2: 1<LOT<3 (N=2265) Control: LOT=0 (N=2835)	Loss more than 3 teeth did not lead to an elevated risk for incident T2DM Adjusted HR=0.98 95%CI 0.69-1.39 Loss 1 or 2 teeth did not lead to an elevated risk for incident T2DM. Adjusted HR=1.02 95%CI 0.79-1.32

Kebede 2017[66]	Germany, SHIP study 11.1y FU (1997-2012)	T2DM: Self-reported physician diagnosed T2DM or treatment with antidiabetic medication	Exposure: mean PPD 2.70–7.25mm (N=NA) Control: mean PPD 0.95–1.97 mm (N=NA)	Deeper PPD did not lead to an elevated risk for incident T2DM. Adjusted incidence RR= 1.271 95% 0.782–2.065
			Exposure: mean CAL 3.15-12.25mm (N=NA) Control: mean CAL 0–1.15mm (N=NA)	Higher CAL did not lead to an elevated risk for incident T2DM. Adjusted incidence RR= 0.819 95%CI 0.489–1.370
Miyawaki 2016[67]	Japan, My health up Study, all male 5y FU (2004-2009)	T2DM: self-reported T2DM and received anti-diabetes medications, or based on clinical test (FBG≥126mg/dl or HbA1C≥6.5%)	Exposure: self-reported tooth loosening (N=262) Control: without tooth loosening (N=2207)	Tooth loosening led to a 73% elevated risk for incident T2DM. Adjusted RR=1.73, 95%CI 1.18–2.53
			Exposure: self-reported gingival bleeding (N=795) Control: without gingival bleeding (N=1674)	Gingival bleeding led to a 23% elevated risk for incident T2DM, but was not statistically significant. Adjusted RR=1.23, 95%CI 0.90–1.70
Morita 2012[68]	Japan, 5y FU (1997-2006)	T2DM: HbA1c≥6.5%	Exposure1: CPI=4 (N=1634) Exposure2: CPI=3 (N=4114) Control: CPI=0 (N=1647)	CPI=4 led to a 245% elevated risk for incident T2DM. Adjusted RR=3.45, 95%CI 1.08-11.02, p=0.037 CPI=3 led to a 145% elevated risk for incident T2DM, but was not statistically significant. Adjusted RR=2.47, 95%CI 0.78–7.79, p=0.122
Myllymki 2018[70]	Finland, Cohort 1935 Survey,	T2DM: WHO 1995 criteria	Exposure1: PPD=4-5mm (N=98)	Both two exposures did not increase the T2DM incidence.

	15-18y FU (1990-2008)		Exposure2: PPD>6mm (N=91) Control: No deep pockets (N=88)	4-5mm PPD: adjusted RR=1.32, 95%CI 0.69–2.53, p>0.05 >6mm PPD: adjusted RR=1.56, 95%CI 0.84–2.92, p>0.05
Winning 2016[71]	UK, PRIME study 7.8y FU (2001-2010)	T2DM: FBG≥126mg/dl and WHO criteria	Exposure1: moderate PD Exposure2: severe PD Moderate/severe PD total=553 Control: No significant PD (N=778) PD severity was based on CDC/AAP classification	Moderate PD led to a 53% elevated risk for developing T2DM, but was not statistically significant. Adjusted RR=1.53, 95%CI 0.86–2.74, p>0.05 Severe PD led to an 85% elevated risk for developing T2DM Adjusted RR=1.85, 95%CI 1.06–3.22, p<0.05

PD: periodontitis; T2DM: type 2 diabetes mellitus; CAL: clinical attachment loss; PPD: periodontal pocket depth; LOT: loss of teeth; OGTT: oral glucose tolerance test; HbA1c: glycated haemoglobin; FBG: fasting plasma glucose; CI: confidence intervals; OR: odds ratio; RR: risk ratios; HR: hazard ratio; CPI: community periodontal index; RPI: Russell periodontal index

Supplementary File Legend

Appendix Tables

Appendix Table 1 Characteristics of included cross-sectional studies

Appendix Table 2 Characteristics of included case-control studies

Appendix Table 3 Summary of trim and fill method

Appendix Figures

Appendix Figure 1 Influence analyses of cross-sectional studies (a) Results of crude OR (b) Results of adjusted OR on T2DM prevalence (c) Results of adjusted OR on PD prevalence (d) Results of crude CAL (e) Results of crude PPD (f) Results of crude NOT (g) Results of crude LOT

Appendix Figure 2 Influence analyses of cohort studies (a) The impact of T2DM on PD incidence (b) The impact of mild PD on T2DM incidence (c) The impact of severe PD on T2DM incidence

Figures

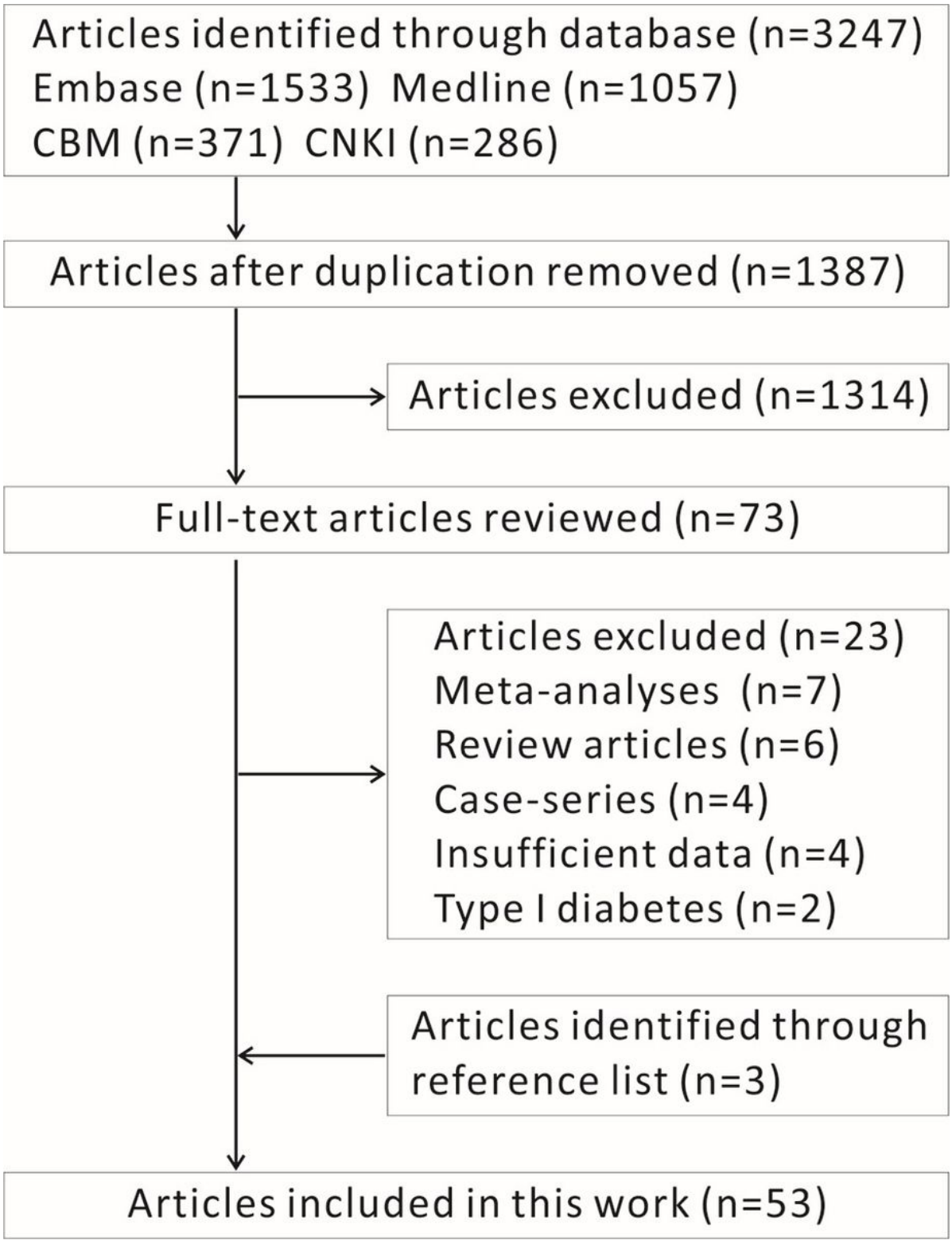

Figure 1

Flow-chart of study selection

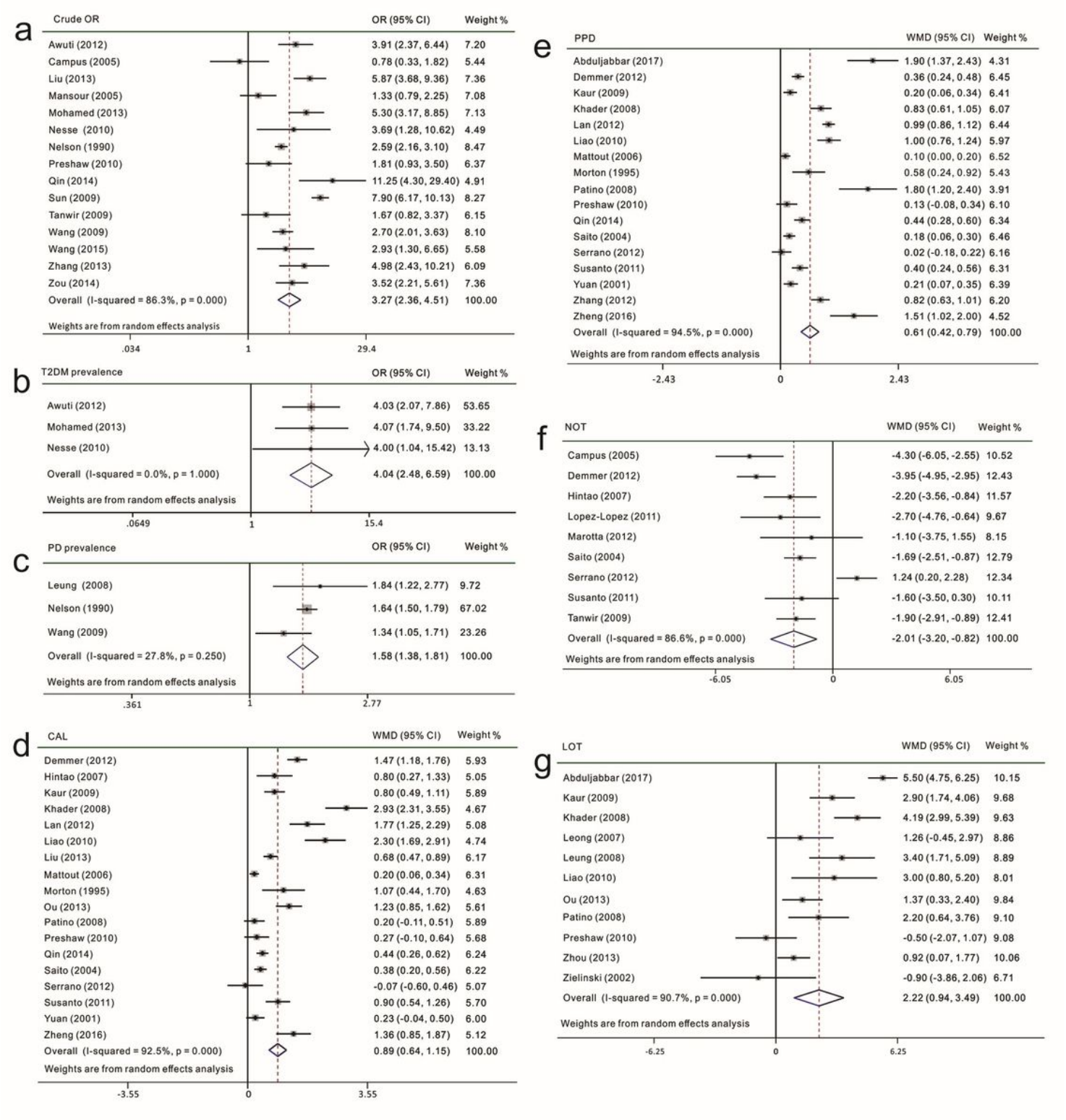

Figure 2

Meta-analyses of cross-sectional studies. (a) Results of crude OR (b) Results of adjusted OR on T2DM prevalence (c) Results of adjusted OR on PD prevalence (d) Results of crude CAL (e) Results of crude PPD (f) Results of crude NOT (g) Results of crude LOT

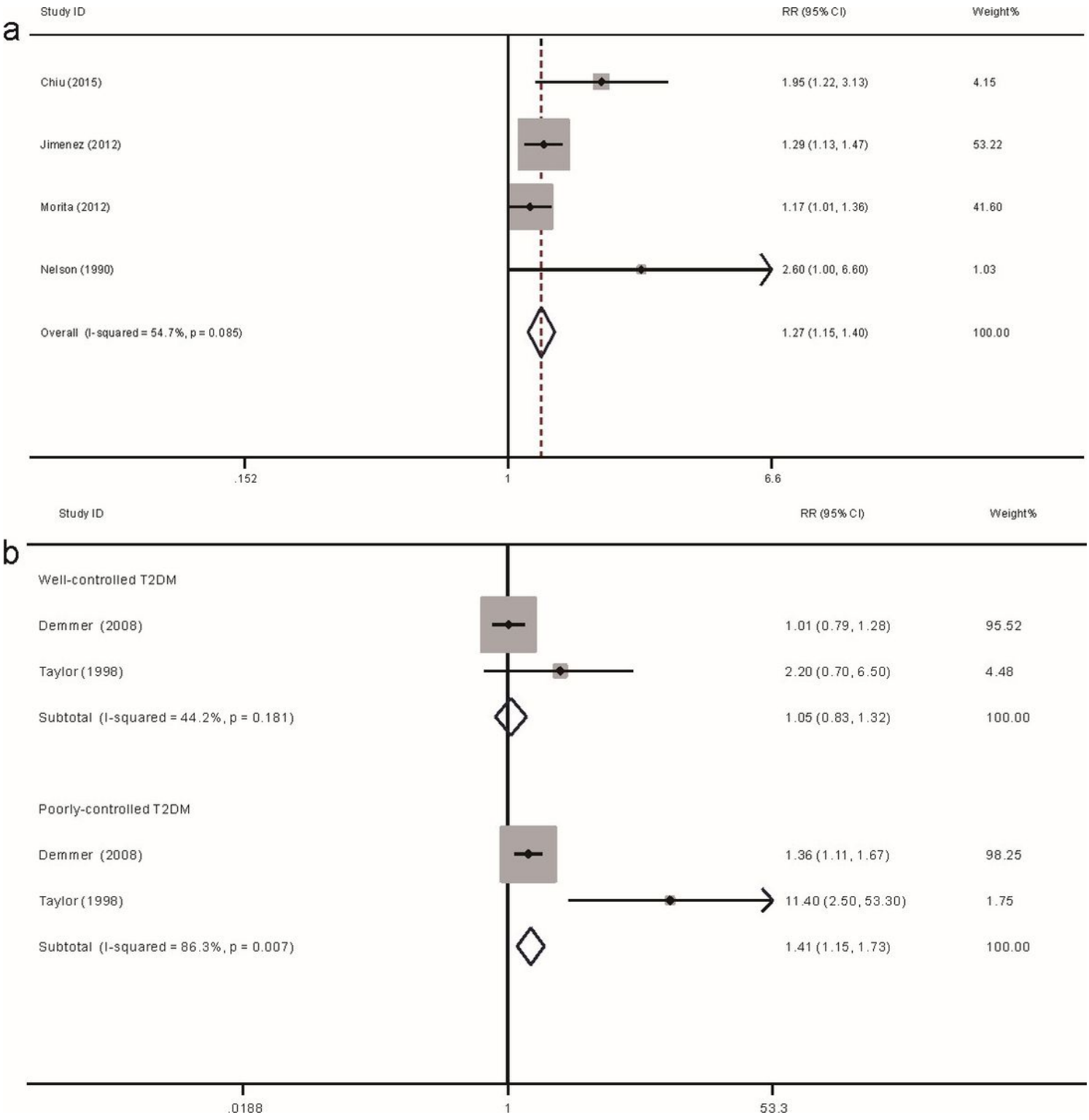

Figure 3

The impact of T2DM on PD incidence. (a) Meta-analysis on PD incidence (b) Meta-analysis on PD incidence based on glycemic control state

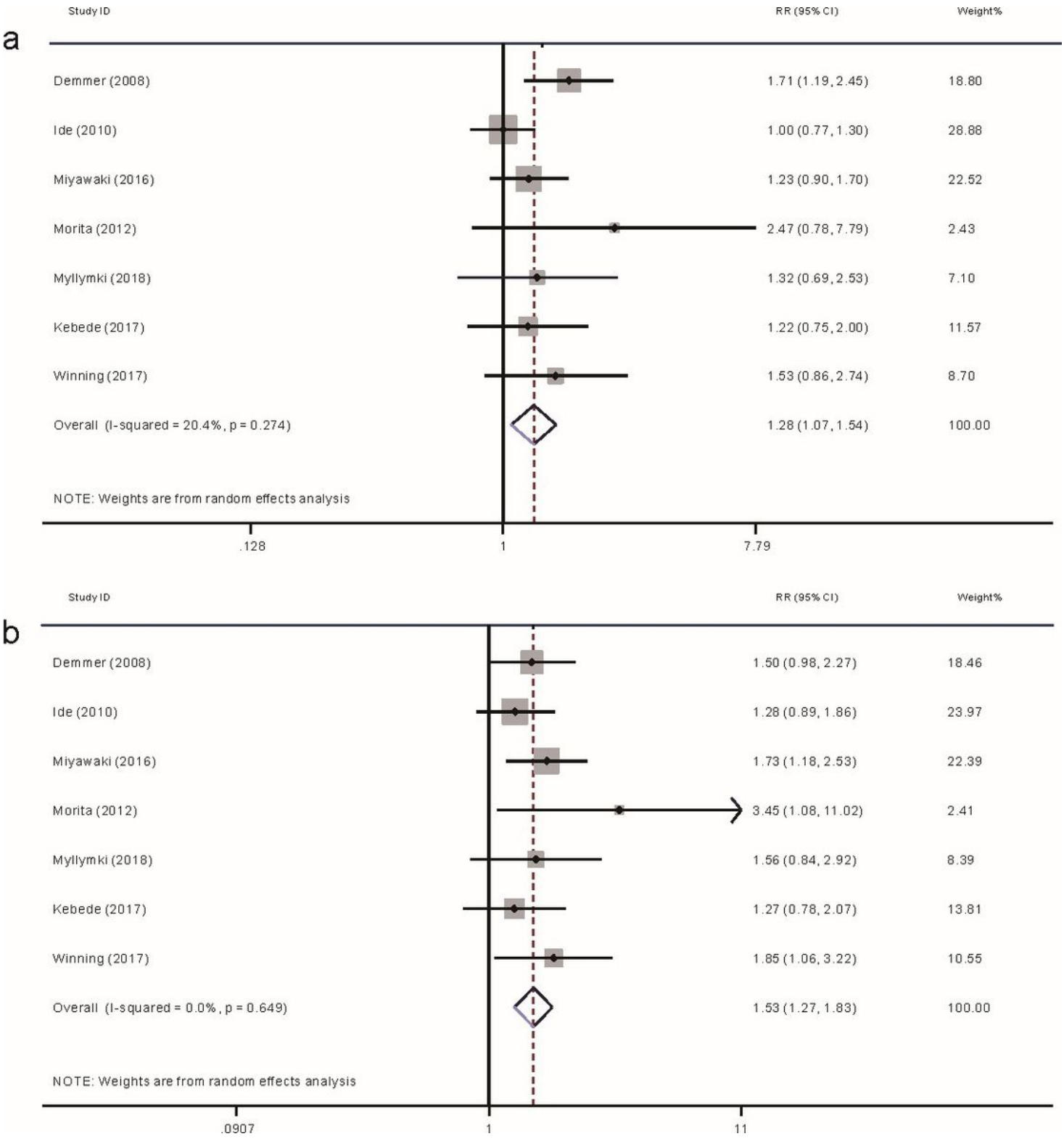

Figure 4

The impact of PD on T2DM incidence. (a) Meta-analysis based on mild PD (b) Meta-analysis based on severe PD

Supplementary Files

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- supplement1.docx
- supplement2.tif
- supplement3.tif