

# Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence

Wenche S. Borgnakke<sup>1</sup>,  
Pekka V. Ylöstalo<sup>2,3,4</sup>,  
George W. Taylor<sup>5</sup> and  
Robert J. Genco<sup>6</sup>

<sup>1</sup>University of Michigan School of Dentistry, Ann Arbor, MI, USA; <sup>2</sup>Department of Periodontology and Geriatric Dentistry, Oulu University Institute of Dentistry, Oulu, Finland; <sup>3</sup>Institute of Dentistry, University of Eastern Finland, Finland; <sup>4</sup>Kuopio University Hospital, Unit for Maxillofacial and Oral Surgery, Kuopio, Finland; <sup>5</sup>Department of Preventive and Restorative Dental Sciences, University of California San Francisco, San Francisco, CA, USA; <sup>6</sup>Departments of Oral Biology and Microbiology, Schools of Dental Medicine and Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY, USA

Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence.

## Abstract

**Background:** Periodontal disease and diabetes mellitus are common, chronic diseases worldwide. Epidemiologic and biologic evidence suggest periodontal disease may affect diabetes.

**Objective:** To systematically review non-experimental, epidemiologic evidence for effects of periodontal disease on diabetes control, complications and incidence.

**Data sources:** Electronic bibliographic databases, supplemented by hand searches of recent and future issues of relevant journals.

**Study eligibility criteria and participants:** Longitudinal and cross-sectional epidemiologic, non-interventional studies that permit determination of directionality of observed effects were included.

**Study appraisal and synthesis methods:** Four reviewers evaluated pair-wise each study. Review findings regarding study results and quality were summarized in tables by topic, using the PRISMA Statement for reporting and the Newcastle-Ottawa System for quality assessment, respectively. From 2246 citations identified and available abstracts screened, 114 full-text reports were assessed and 17 included in the review.

**Results:** A small body of evidence supports significant, adverse effects of periodontal disease on glycaemic control, diabetes complications, and development of type 2 (and possibly gestational) diabetes.

**Limitations:** There were only a limited number of eligible studies, several of which included small sample sizes. Exposure and outcome parameters varied, and the generalizability of their results was limited.

**Conclusions and implications of key findings:** Current evidence suggests that periodontal disease adversely affects diabetes outcomes, and that further longitudinal studies are warranted.

Webcast: A brief video summarizing this review may be viewed for free at:  
<http://www.scivee.tv/journalnode/58235>.

Key words: diabetes complications; diabetes mellitus; gestational diabetes; epidemiology; haemoglobin a, glycosylated; humans; periodontal diseases; review, systematic

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Periodontal diseases, including the reversible form gingivitis, affect up to 90% of the world's population (Pihlstrom et al. 2005). While “dental car-

ies of permanent teeth” tops the Global Burden of Disease (GBD) list with an estimated prevalence of 35.3%, chronic periodontitis (10.8%) follows with only headache/migraine and skin diseases between (Vos et al. 2013). Periodontitis is reported to affect half of adults (Hu et al. 2011,

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Eke et al. 2012a, Patel & Platform for Better Oral Health in Europe, 2012) or more (Holtfreter et al. 2010), with the severe form periodontitis affecting around 10% (range: 5–20%) of adults (Petersen et al. 2005, Dye et al. 2007, Eke & Dye 2009, Holtfreter et al. 2009, Mattila et al. 2010, Eke et al. 2012a, Patel 2012, White et al. 2012) and moderate periodontitis around one-third (Holtfreter et al. 2009, Eke et al. 2012a, White et al. 2012). In aged populations and in indigenous people, the prevalence of periodontitis is even higher: It is reported that 70–90% of individuals aged 60–74 years (Holtfreter et al. 2010, Mattila et al. 2010, Patel 2012) and indigenous people (Brothwell & Ghiabi 2009) suffer from periodontitis. It is noteworthy the actual prevalence of periodontitis may be substantially higher than hitherto reported. This is due to underestimation by prior population surveys due to their use of partial mouth recordings and reliance on only periodontal probing depth instead of clinical attachment level (Albandar & Rams 2002, Eke et al. 2010, 2012b, Beltran-Aguilar et al. 2012, White et al. 2012).

It is estimated that 346 million people have diabetes worldwide (World Health Organization 2011) with the prediction of 439 million by the year 2030, representing an increase of 54% in 20 years to encompass almost one tenth of adults 20 years and older (Chen et al. 2012). In addition, according to the Global Burden of Disease study, diabetes is a major cause of years lived with disability (YLD), estimated at 20.8 million YLDs. Diabetes is ranked as the ninth most common disorder in the world, amassing a 67.2% increase over the 20 years from 1990 to 2010 (Vos et al. 2013).

From a global perspective, although the prevalence of diabetes is high in the industrialized countries – with for example 11.3% (25.8 million) of the US population already having diabetes (Centers for Disease Control & Prevention 2011) – it is worth emphasizing that over 80% of diabetes patients live in low- and middle-income countries (World Health Organization 2011), with the Middle East encompassing six of the ten countries with the highest prevalence (International Diabetes Federation 2011).

Currently, there is increasing interest in links between periodontal disease and non-oral, systemic, inflammatory-related diseases and conditions, such as atherosclerotic cerebro-cardiovascular conditions and events (Kebschull et al. 2010, Ylöstalo et al. 2010, Borgnakke 2012, Lockhart et al. 2012). The biologic plausibility supporting such connection is based on the fact that inflammatory periodontal disease due to reaction to pathogenic biofilm stimulates a chronic systemic inflammation and thus contributes to the cumulative inflammatory burden in the host (Loos 2005, Renvert et al. 2006). Inflammation precedes diabetes onset (Duncan et al. 1999, Schmidt et al. 1999, Duncan & Schmidt 2006) and is linked to insulin resistance and development of diabetes (Wang et al. 2013) as well as its complications (King 2008). Since effective therapy and management of periodontal disease are well established, it is important to know for future prevention and control of diabetes whether periodontitis indeed plays a role in the development and control of diabetes and its potentially fatal complications (Lalla & Papapanou 2011).

If such a causal relation indeed exists, a new paradigm in dental and medical standard of care for screening, prevention and management of diabetes could be developed in the future. Close collaboration among each patient's health care professionals would be warranted, especially among medical and dental care providers (Glurich et al. 2013).

## Review of Current Literature

### Objective

Our aim was to conduct a systematic review to identify and evaluate the scientific evidence from epidemiologic, non-experimental, observational studies of effects of periodontal disease on diabetes mellitus. Specifically, we explored effects on glycaemic control, the development of complications and the onset of diabetes. Study populations should consist of individuals without diabetes and with known types 1 and 2 diabetes, in addition to pregnant women with and without gestational diabetes.

*The specific questions addressed in this systematic review were:*

1. Do people with manifest type 2 diabetes, pre-diabetes or no known diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?
2. Do people with type 1 diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?
3. Do people with diabetes, who have poorer periodontal health, have more diabetes complications than those with better periodontal health?
4. Do people without known diabetes, who have poorer periodontal health, have greater risk for developing (incident) type 2 diabetes than those with better periodontal health?
5. Do women with gestational diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?
6. Do pregnant women, who have poorer periodontal health, have greater risk for gestational diabetes than those with better periodontal health?

Only reported findings from original, epidemiologic, non-intervention, observational studies of longitudinal, case-control or cross-sectional designs were eligible for inclusion in this review. They needed to include different categories of periodontal disease (exposure) and at least one parameter related to diabetes (outcome).

## Methods

### Protocols

*The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)*

For describing and summarizing the results of our review, we used the 27 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement; [www.prisma-statement.org](http://www.prisma-statement.org)) (Moher et al. 2009a,b).

*The Newcastle-Ottawa Scale for assessing the quality of non-randomized studies (NOS)*

Assessment of the quality of non-randomized, non-interventional studies is essential for proper evaluation

of the evidence provided by each study. We followed the Newcastle-Ottawa System (NOS) protocol (Wells et al. 2011). The scale is described and the forms used displayed in the online appendix, Exhibits Appendix S6 and Appendix S7–S9 respectively.

#### Eligibility criteria

We limited our search to original research reports on periodontal disease and diabetes that were conducted in humans and reported in English in any year.

#### Information sources

We searched electronic databases and hand searched bibliographies of already identified reports, as well as online sites with reports accepted for publication ahead of print for the most relevant scientific journals. We also created automated electronic alerts for identification of additional reports. In addition, we contacted authors for clarification and additional information regarding three papers. We conducted the last comprehensive search on July 26, 2012, but ensured by the last search on January 6, 2013, that no additional eligible reports were catalogued in PubMed. While imposing the limits Humans and English language, we searched the following bibliographic databases:

- PubMed, incl. MEDLINE and Pre-MEDLINE, by OVID (from 1950)
- Web of Science by Thomson Reuters
- EMBASE by Elsevier via OVID (from 1980)
- Dentistry and Oral Sciences Source™ by EBSCO via OVID
- CINAHL® by EBSCO (from 1937)
- Evidence Based Medicine (EBM) Reviews
- SciVerse by Elsevier
- LILACS (Latin American and Caribbean Health Sciences) by Virtual Health library (from 1982)

Further details regarding these databases searched are provided in Appendix S1.

#### Literature search

We searched the different databases using as identical search strategies as possible within the rules of each database. As an example, the main PubMed search query follows, in which “tiab” means the terms may be found in the title, the abstract or both: (“periodontal diseases”[mh] OR periodontium[mh] OR periodontics[mh] OR periodont\*[tiab]) AND (“diabetes mellitus”[mh] OR “diabetes insipidus”[mh] OR diabet\*[tiab] OR “dm 1”[tiab] OR “dm i”[tiab] OR “dm 2”[tiab] OR “dm ii”[tiab] OR “hemoglobin a, glycosylated”[mh] OR a1c[tiab] OR “hb a1c”[tiab] OR hba1c[tiab] OR “blood glucose”[mh] OR “blood sugar”[tiab] OR ((glucose[ti] OR sugar[ti]) AND (level[ti] OR control[ti])) OR hyperglycemia[mh] OR hypoglycemia[mh] OR glycemi\*[tiab] OR glycaemi\*[tiab] OR hyperglyc\*[tiab] OR hypoglyc\*[tiab]). Filters used were: Humans and English language.

It was confirmed that addition of the UK spelling of the key search terms provided results identical to the search using US spelling alone. In addition to the example shown, this was ensured by extra searches using the term “haemoglobin.”

The electronic bibliographic reference manager program EndNote, version X6, by Thomson Reuters (<http://endnote.com/>) was used to identify duplicates; screen citations and abstracts; categorize citations in ineligible and eligible groups; create lists of citations for tables; and create the in-text citations and the bibliography.

#### Study selection

We identified 4990 citations that included the search terms, amounting to 2246 unique citations after identifying and removing duplicate records. Two of the authors reviewed the 2246 citations and their abstracts and selected 114 reports for reading of the full text. The four reviewers read the papers in alternating pairs, so that each reviewer read half (57) papers each, but with different partners. Hence, each report was scored independently by two reviewers. In case of discrepancies, all four reviewers were asked to review the papers,

without knowledge of the other reviewers’ decisions. All four reviewers arrived at a final, mutual agreement of scoring each paper based on discussions during frequent telephone conference calls. This procedure was followed for both classification of eligibility and quality of reports deemed eligible for inclusion.

We selected reports on original epidemiologic, non-interventional, observational (descriptive and analytical) studies that concerned parameters on periodontal disease and glycaemic control or blood concentrations of glucose among people without diabetes or with any kind of diabetes (no pathological elevation in blood glucose concentration, pre-diabetes (impaired fasting glucose), types 1 or 2 diabetes and gestational diabetes). For cohort and case-control studies, it must be evident that the topic studied was the effect of periodontal disease on diabetes, that is, the report results must permit determination of directionality. In addition, cross-sectional studies were eligible for inclusion, but only if they reported on associations between periodontal disease (exposure) and diabetes parameters (outcomes) that were unlikely to cause periodontitis, such as the diabetes complications retinopathy and neuropathy, to ensure determination of directionality.

#### Data collection process

We developed forms for scoring each report as well as for the logistic administration, logging and track keeping of papers to retrieve and to review. One reviewer (WSB) assumed the administrative tasks in addition to the full reviewer tasks and created a Master file with the 114 citations that were numbered for unambiguous identification. This Master file was used to identify the assignments of reports among the four reviewers, to enter the scores from each reviewer as they became available, and to identify discrepancies between the duplicate reviewers’ categorization. Subsequently, the Master file would be used for tallying the number of reports in the different categories of eligibility and ineligibility.

Prior to actual scoring, the rating forms were tested by all reviewers by trial scoring 21 relevant papers that

the administrative reviewer already had available before the actual systematic search. The scoring forms were discussed and revised in an iterative process until all four reviewers agreed on the final format.

The data extraction was performed in duplicate with two reviewers independently assessing each report, determining eligibility and indicating reasons for ineligibility.

First, each reviewer decided on a study's eligibility for inclusion in the systematic review, based on the reported parameters. At this point, the reviewer made no quality assessment of the study. Each report deemed *ineligible* for inclusion was categorized in a hierarchical manner according to one of the following main reasons for its exclusion:

Main Exclusion Reasons (in Hierarchally Prioritized Order):

- N1. Not original study (review, guidelines, comment)
- N3. Original, but not epidemiologic study
- N4. Original, but interventional study
- N2. Original study, but not on effect of periodontal disease on glycaemic control
- N5. Other reason.

The ineligible study was recorded with the exclusion reasons on the form displayed in Exhibit Appendix S2.

Second, the reports deemed eligible were categorized into one of the following groups:

Eligibility Categories for Effect of Periodontal Disease on:

- E1. Glycaemic control in:
  - E1a. Type 2 diabetes
  - E1b. Pre-diabetes
  - E1c. No known diabetes
- E2. Glycaemic control in type 1 diabetes
- E3. Diabetes-related complications
- E6. Incident type 2 diabetes (new diabetes developed in individuals without diabetes at baseline)
- E4. Gestational diabetes control
- E5. Risk for [development of] gestational diabetes

Third, data were extracted from each paper by each reviewer who

recorded the findings on the data collection form displayed as Exhibit Appendix S4.

#### Data items

Regardless of study design, we collected the following information, with the majority of data points equipped with standard response categories with the option for open-ended responses: Study Design, Population Based, Study Duration, # Subjects, Sex, Age, DM Type, DM outcomes assessed, DM Measured/Diagnosed, DM Control Definition/Groups, Other DM-Related Measures, Type of Periodontal Examination, Periodontal Measures, Periodontal Case Definition/Groups, Examiner Calibration, Analysis, Effect of Perio on DM, Effect: Parameter & Size, Dose-Response Effect, Main Findings and Comments (Medication use; Comorbidity, etc.), Exhibit Appendix S4.

#### Risk of bias in individual studies

As mentioned, we assessed the quality of each cohort and case-

control study according to NOS for Assessing the Quality of Non-randomized Studies (Wells et al. 2011), described in Exhibit Appendix S6, but devised an additional scale for rating cross-sectional studies. The NOS evaluates three dimensions of a study, namely A) selection of the study groups; B) comparability of the study groups; and C) ascertainment of either the exposure or outcome of interest. We developed one form for each of the three study designs: cohort, case-control and cross-sectional. The three forms are displayed as Exhibits Appendix S7-S9.

Using these forms, we rated each report at both the study and outcome levels.

#### Summary measures

The majority of studies reported results using odds ratios (OR), hazard ratios (HR) and hazard rate ratios (HRR), but also other relative risks measures, such as risk ratios, rate ratios or relative risks.

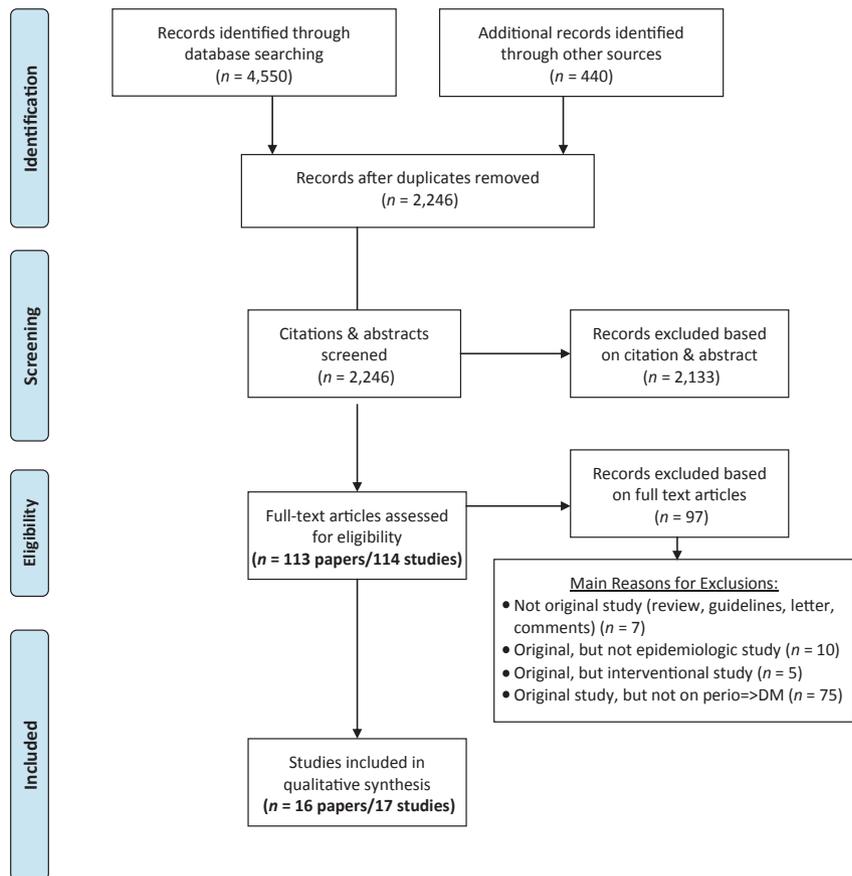


Fig. 1. Selection of studies for systematic review of epidemiologic observational evidence for the effect of periodontal disease on diabetes control, complications and incidence.

Table 1. The 16 reports (on 17 studies) included in the final review: citations

1. Abrao, L., Chagas, J. K. & Schmid, H. (2010) Periodontal disease and risk for neuropathic foot ulceration in type 2 diabetes. *Diabetes Res Clin Pract* **90**, 34–39. doi:10.1016/j.diabres.2010.06.014.
2. Dasanayake, A. P., Chhun, N., Tanner, A. C., Craig, R. G., Lee, M. J., Moore, A. F. & Norman, R. G. (2008) Periodontal pathogens and gestational diabetes mellitus. *J Dent Res* **87**, 328–333. doi:10.1177/154405910808700421.
3. Demmer, R. T., Desvarieux, M., Holtfreter, B., Jacobs, D. R., Jr., Wallaschofski, H., Nauck, M., Volzke, H. & Kocher, T. (2010) Periodontal status and A1C change: longitudinal results from the study of health in Pomerania (SHIP). *Diabetes Care* **33**, 1037–1043. doi:10.2337/dc09-1778.
4. Demmer, R. T., Jacobs, D. R., Jr. & Desvarieux, M. (2008) Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. *Diabetes Care* **31**, 1373–1379. doi:10.2337/dc08-0026.
5. Ide, R., Hoshuyama, T., Wilson, D., Takahashi, K. & Higashi, T. (2011) Periodontal disease and incident diabetes: a seven-year study. *J Dent Res* **90**, 41–46. doi:10.1177/00220345110381902.
6. Li, Q., Chalmers, J., Czernichow, S., Neal, B., Taylor, B. A., Zoungas, S., Poulter, N., Woodward, M., Patel, A., de Galan, B., Batty, G. D. & ADVANCE Collaborative Group. (2010) Oral disease and subsequent cardiovascular disease in people with type 2 diabetes: a prospective cohort study based on the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial. *Diabetologia* **53**, 2320–2327. doi:10.1007/s00125-010-1862-1.
7. Morita, I., Inagaki, K., Nakamura, F., Noguchi, T., Matsubara, T., Yoshii, S., Nakagaki, H., Mizuno, K., Sheiham, A. & Sabbah, W. (2012) Relationship between periodontal status and levels of glycated hemoglobin. *J Dent Res* **91**, 161–166. doi:10.1177/0022034511431583.
8. Morita, T., Yamazaki, Y., Mita, A., Takada, K., Seto, M., Nishinoue, N., Sasaki, Y., Motohashi, M. & Maeno, M. (2010) A cohort study on the association between periodontal disease and the development of metabolic syndrome. *J Periodontol* **81**, 512–519. doi:10.1902/jop.2010.090594.
9. Noma, H., Sakamoto, I., Mochizuki, H., Tsukamoto, H., Minamoto, A., Funatsu, H., Yamashita, H., Nakamura, S., Kiriya, K., Kurihara, H. & Mishima, H. K. (2004) Relationship between periodontal disease and diabetic retinopathy. *Diabetes Care* **27**, 615. doi:10.2337/diacare.27.2.615.
10. Saito, T., Shimazaki, Y., Kiyohara, Y., Kato, I., Kubo, M., Iida, M. & Koga, T. (2004) The severity of periodontal disease is associated with the development of glucose intolerance in non-diabetics: the Hisayama study. *J Dent Res* **83**, 485–490. doi:10.1177/154405910408300610.
11. Saremi, A., Nelson, R. G., Tulloch-Reid, M., Hanson, R. L., Sievers, M. L., Taylor, G. W., Shlossman, M., Bennett, P. H., Genco, R. & Knowler, W. C. (2005) Periodontal disease and mortality in type 2 diabetes. *Diabetes Care* **28**, 27–32. doi:10.2337/diacare.28.1.27.
12. Shultis, W. A., Weil, E. J., Looker, H. C., Curtis, J. M., Shlossman, M., Genco, R. J., Knowler, W. C. & Nelson, R. G. (2007) Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. *Diabetes Care* **30**, 306–311. doi:10.2337/dc06-1184.
13. Southerland, J. H., Moss, K., Taylor, G. W., Beck, J. D., Pankow, J., Gangula, P. R. & Offenbacher, S. (2012) Periodontitis and diabetes associations with measures of atherosclerosis and CHD. *Atherosclerosis* **222**, 196–201. doi:10.1016/j.atherosclerosis.2012.01.026.
14. Taylor, G. W., Burt, B. A., Becker, M. P., Genco, R. J., Shlossman, M., Knowler, W. C. & Pettitt, D. J. (1996) Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol* **67**, 1085–1093. doi:10.1902/jop.1996.67.10s.1085.
15. Thorstensson, H., Kuylenstierna, J. & Hugoson, A. (1996) Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *J Clin Periodontol* **23**, 194–202. doi:10.1111/j.1600-051X.1996.tb02076.x.
16. Xiong, X., Elkind-Hirsch, K. E., Vastardis, S., Delarosa, R. L., Pridjian, G. & Buekens, P. (2009) Periodontal disease is associated with gestational diabetes mellitus: a case-control study. *J Periodontol* **80**, 1742–1749. doi:10.1902/jop.2009.090250.

### Synthesis of results

Due to the small number of studies for each topic and their pronounced heterogeneity with regard to their design and outcome measures, their data could not be pooled and meta-analyses conducted. Instead, findings from each study were described together with the remaining studies on the same topic, with one Table for each original question posed.

### Risk of bias across studies

As with other bodies of scientific evidence, the potential effect of publication bias, favouring reporting of positive outcomes, cannot be excluded. Likewise, it is not known whether the authors reported only their most favourable results.

### Additional analyses

Pre-review knowledge of the limited scope of the existing evidence pre-

vented pre-specification of any additional analyses to conduct, based on the reported results.

## Results

### Study selection

A total of 2246 unique citations were identified. The numbers of studies screened, assessed for eligibility, undergoing reading of full text, and included in the final review are shown in Fig. 1. Table 1 displays the final 16 papers selected for the review that yielded results from 17 studies, as one report included findings for two different outcomes (Saito et al. 2004). The citations for the 97 reports excluded upon full text perusing are displayed in Exhibit Appendix S3, along with the main reason for exclusion of each paper. Exhibit Appendix S5 lists the 17 reports included in the final review.

### Description of characteristics, results and quality of each study

The findings from this review are described in the following for each of the originally posed questions. For each topic, a table displays the characteristics and findings from each study, and a brief summary is provided of only the longitudinal results, that is, any cross-sectional findings at baseline are not shown. Importantly, all confounders for which the analyses are controlled are displayed for each outcome or model, respectively, in Tables 2–5 under the heading “Confounders Controlled.” In consideration of space and readability, these confounders will not be re-cited in the text. Risk of bias within and across studies is addressed briefly and the consensus NOS quality scores for each study are displayed in the online Appendix, with such tables

corresponding by topic to the results tables included in this main report. All studies were conducted among adults.

*1. Do people with manifest type 2 diabetes; pre-diabetes; or no known diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health? (E1)*

*Brief summary of characteristics and results*

Table 2 displays a summary of the four studies identified. No eligible study was conducted among subjects with baseline pre-diabetes (*Eligibility Category E1b*), so only reports on studies among participants with either manifest type 2 diabetes (*E1a*) or no known diabetes (*E1c*) at baseline were included.

Of the four studies, three were of prospective and one retrospective cohort design. They included 4512 participants ages 18–81 years in three countries (Germany, Japan and USA). Clinical periodontal examination results were reported based on periodontal probing depth (PPD), clinical attachment loss (CAL), gingival bleeding and number of teeth present. Radiographic examination in one study assessed per cent bone loss. Glucose measures included glycosylated haemoglobin (HbA1c) as well as fasting and 2-h 75 g plasma glucose level, and oral glucose tolerance test (OGTT).

One study was conducted among individuals with type 2 diabetes (Taylor et al. 1996) and three in people without diabetes at baseline (Saito et al. 2004, Demmer et al. 2010, Morita et al. 2010). The former included American Indians of the Gila River Indian Community (Pima Indians) and demonstrated that severe periodontitis was associated with poor glycaemic control after a 5-year period. Those with CAL of at least 6 mm had over six times the risk of poor glycaemic control compared to those without; and individuals 35 years and younger at baseline with radiographic bone loss of at least 50% of the root length had 4.2–13.6 times the risk of poor control (Taylor et al. 1996).

Over a 4-year period, initially systematically healthy Japanese employees with periodontal disease were in

a dose–response manner more likely to develop metabolic syndrome (that includes hyperglycaemia) than those periodontally healthy (Morita et al. 2010).

In large population studies in Germany and Japan, the former found that after five years, an increase in mean CAL, but not in PPD, was associated with an increase in HbA1c (Demmer et al. 2010). In addition, individuals with a healthy periodontium at both baseline and follow-up had less HbA1c increase than those with poor baseline and 5-year deterioration in periodontal health (0.005 versus 0.143%;  $p = 0.003$ ).

However, the latter demonstrated after 10 years a significant increase in impaired glucose tolerance (IGT) with mean PPD, but not CAL, with each additional millimetre mean PPD corresponding to 0.13% increase in HbA1c (Saito et al. 2004).

*Quality assessment*

All studies used multivariate analyses, and all controlled for age and smoking, except for one study (Taylor et al. 1996). All four studies earned eight or nine of the nine possible stars in the NOS quality rating as shown in Appendix S10.

*Major weaknesses*

There were very few studies. They were conducted only in Germany, Japan and USA and were not generalizable. All clinical studies used partial mouth periodontal examinations. Periodontal and metabolic outcome parameters varied.

*2. Do people with type 1 diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?*

No studies were found eligible (E2).

*3. Do people with diabetes, who have poorer periodontal health, have more diabetes-related complications than those with better periodontal health?*

*Brief summary of characteristics and results*

The seven studies are summarized in Table 3 (E3). They were conducted in Brazil, Japan, Sweden, USA (3) and in 20 different countries respectively. Four were of cohort and three of cross-sectional design. Only one study

focused on type 1 diabetes, five studied type 2 diabetes, and one did not specify diabetes type. A total of 18,397 subjects participated, ranging from 39 to 10,958, with five of the studies combined including 1391 persons. Participants were at least 25 years old.

Clinical periodontal examination results were reported based on PPD and CAL, bleeding on probing; and number of teeth present. Radiographic examinations assessed per cent bone loss. In the multi-country study, self-reported number of teeth present and number of days with gingival bleeding the past year were described. Diabetes-related complications encompassed retinopathy; nephropathy (macroalbuminuria, proteinuria and end-stage renal disease); neuropathic foot ulceration; cardiovascular disease (coronary heart disease, ischaemic heart disease, carotid intima media thickening and calcification of atherosclerotic plaque); cerebrovascular events (stroke); and death due to cardiorenal disease.

In the study among people with type 1 diabetes, all cardiorenal complications, but not retinopathy, were significantly associated with periodontal disease (PD). All studies in subjects with types 1 and 2 diabetes found that those with periodontal disease, especially severe disease, and edentulism, had higher risk for diabetes-related complications than participants without or with mild periodontal disease. A dose–response effect was seen between severity of periodontal disease and complications. For instance, moderate and severe PD, as well as edentulism significantly predicted both macroalbuminuria and end-stage renal disease in a dose-dependent manner among Pima Indians (Shultis et al. 2007). In this population, those with severe PD had 3.5 times higher risk for cardiorenal death; moreover, nephropathy and death from ischaemic heart disease were significantly predicted by PD (Saremi et al. 2005).

*Quality assessment*

Two studies used full-mouth and four partial mouth clinical periodontal examinations, and radiographic bone loss assessment was performed in four studies, of which three used all teeth. The seventh

Table 2. Effect of periodontal disease on metabolic control in subjects with type 2 diabetes or without diabetes (E1a & E1c)

Author	A) # Subjects:		OUTCOME				
	a. Perio Cases		Metabolic	Effect on			
Year	b. Comparison	EXPOSURE	Control	Metabolic	Effect Size:		
Country	group(s)	Perio Measure	Measure	Control?	Odds Ratio (OR), Trend	Effect on Metabolic	
Study Design	B) Age	&	&	&	&	Control/	Confounders
BL DM Type	C) Study Duration	Case Definition	Definition	Generalisable?	Significance (95%CI)	Conclusion	Controlled
<b>E1a. Type 2 Diabetes (DM2):</b>							
Taylor et al. 1996 USA Cohort DM2	A1) X-ray Exams: N=105(31M+74F), incl. 88 w/≥2 exams	Partial mouth (6 index teeth) • PPD • CAL	• OGTT • HbA1c	Yes, stat. sign. in Pima American Indians in the Gila River Indian Community, Arizona, USA	OR for Poor Glycaemic Control by Baseline Age: 1) Bone Loss: • 25yrs: OR=13.6 (1.7- 106.0) • 30yrs: OR=7.3 (1.5-38.2) • 35yrs: OR 4.2 (1.2- 14.9) • 40yrs: OR=2.3 (0.8-6.8) • 45yrs: OR=1.3 (0.4-4.0) • 50yrs: OR=0.7 (0.2-2.9)	Severe periodontitis was associated with poor metabolic control in type 2 diabetes after 2 to 5 years	1) Bone loss: • Age • Hba1c @ BL 2) CAL: • smoking • diabetes severity • diabetes duration Multivariate
	A2) Clin. Exams: N=89(27M+62F) B) All ≥18yrs [18-67yrs] C1) X-ray Exams: 2.4yrs [2-4yrs] C2) Clin. Exams: 5yrs	• X-ray bone loss PD@BL: >1 tooth with: 1) X-ray bone loss ≥50% or 2) CAL≥ 6 mm	Control: HbA1c ≥9%: Poor	Not generalisable	Severe vs. no periodontitis: OR=6.2 (1.5-25.3)		
COMMENTS: Good examiner calibration agreement for clinical & radiographic examinations							
<b>E1c. No Diabetes:</b>							
Morita et al. 2010 Japan Cohort No DM No MetS	A) N=1,023 (727M+296F) B) 37.3yrs [20-56yrs] C) 4yrs	Partial mouth (sextants) CPI Codes: 0: healthy 1: bleeding 2: calculus 3: ≥1 PPD 4-5mm 4: ≥1 PPD> 6mm PD Groups: CPI ≤ 2 vs. CPI ≥ 3	• Incidence of metabolic syndrome (association w/PD) • HbA1c • fasting glucose • OGTT	Yes, stat. sign. in (71% male) Japanese employees under 60 years	OR=1.6 (1.1-2.2; p<0.05) for ≥1 positive MetS component vs. no positive MetS component in PD; OR=1.4 (1.0-2.1) for ≥1; OR=2.2 (1.1-4.1) for ≥2 MetS components	In initially healthy individuals, periodontal disease is associated in a dose-response manner with development of ≥1 components of metabolic syndrome over 4 years	• age • gender • cigarette smoking • exercise • eatingbtw. meals • weight at BL Multivariate
COMMENTS: No examiner calibration; Dose-response effect stat. sign for trend; CPI is a poor measure of PD							
Demmer et al. 2010 Germany (Pomerania) Cohort No DM	A) N=2,793 (47%M+53%F) a1) 488 a2) 463 a3) 479 a4) 241 b) 1,122 B) 48(±15)yrs [20-81yrs] C) 5yrs	Perio Exam: Partial mouth* Tooth count: Full mouth ≤28 teeth • PPD • CAL • # teeth PD groups based on% BL sites w/CAL>5mm: a1) 1-8% a2) 9-33% a3) 34-100% a4) Edentulous b) 0%	• HbA1c	Yes, stat. sign. in Caucasians in Pomerania in former East Germany	1) BL # teeth was not consistently associated with 5yr change in HbA1c (P <sub>trend</sub> =0.84) 2) Those perio healthy at BL & FU had less 5yr HbA1c change than those w/poor BL perio health and 5yrs perio deterioration: 0.005 vs. 0.143% (p=0.003)	5-year change in mean CAL (but not in mean PPD) was associated with HbA1c change	• age • waist/hip ratio • systolic BP • triglycerides • physical activity • white blood cellcount • fibrinogen • hsCRP • sex • region • smoking • education

Table 2. (continued)

	A) # Subjects:		OUTCOME				
Author	a. Perio Cases		Metabolic	Effect on			
Year	b. Comparison	EXPOSURE	Control	Metabolic	Effect Size:		
Country	group(s)	Perio Measure	Measure	Control?	Odds Ratio (OR), Trend	Effect on Metabolic	
Study Design	B) Age	&	&	&	&	Control/	Confounders
BL DM Type	C) Study Duration	Case Definition	Definition	Generalisable?	Significance (95%CI)	Conclusion	Controlled
		Used 3 additional PD groupings based on:					• education
		1) BL PPD					• family DM history
		2) BL # teeth					Multivariate linear regression
		3) 5yr change in % sites w/CAL <sub>≥</sub> 5mm					
COMMENTS: Study of Health In Pomerania (SHIP); *right or left side of mouth; Good to excellent agreement in intra- and inter-examiner periodontal exam calibration							
Saito et al. 2004	All without DM @BL in 1988	Partial mouth**	• 2hr 75g OGTT (BL)	Yes, stat.sign. in Japanese (Hisayama)	1) High vs. Low PPD categories: OR=2.4 (1.4-2.6; p= 0.009) for risk of IGT	1) Proportion w/IGT increased significantly	• age
Japan	A) @ FU in 1998:	• CAL	• IGT	40-79yrs community dwellers	2) No sign. increase in IGT with mean CAL	w/mean PPD	• smoking
Retrospective Cohort*	N1=961 (377M+584F)	PD-1: Mean DDP:	• HbA1c	Not generalisable		2) Those w/normal BL GT who developed IGT over 10 years were sign. more likely to have deep PPD, but not CAL, at FU	• BMI
No DM	N2=591=those among N1 aged ≥40yrs in 1988	a1) Intermediate: 1.3-2.0mm	• Incident Glucose Intolerance: NGT in 1988& IGT in 1998			3) Each additional mm mean PPD corresponded to 0.13% HbA1c increase (p=0.007)	• exercise
	N3=545 w/HbA1c values both at BL and FU	PD-2: Mean CAL:	• Glucose Intolerance progression=			4) Severity of perio-dontal disease expressed as PPD, but not CAL, was sign. associated with development of glucose intolerance	• alcohol
	A) 40-79 yrs	a2) High: >2.5mm					
	B) 10 yrs	b) Low: <1.5mm					

COMMENTS: \*May be regarded as 1998 cross-sectional exam plus 1988 OGGT data, i.e., oral health data only from 1998 (not from BL 1988); \*\*NHANES III protocol (1 max. + 1 mand. quadrant); 4 “trained” examiners; No calibration reported

BP, Blood Pressure; CPI, Community Periodontal Index; Excl., Excluding/Excluded; MetS, Metabolic Syndrome; Perio, Periodontal/Periodontally; #, Number (of); &, and; BL, Baseline/Beginning of Study Period; CAL, Clinical Attachment Loss; CI, Confidence Interval; CPI, Community Periodontal Index; DM, Diabetes Mellitus; DM2, Type 2 Diabetes Mellitus; F, Female; FU, Follow-Up/End of Study Period; GT, Glucose Tolerance; HbA1c, Glycosylated(Glycated) Haemoglobin; hr, hour; HR, Hazard Ratio; hsCRP, high-sensitivity C-reactive protein; IGT, Impaired Glucose Tolerance; M, Male; NGT, Normal Glucose Tolerance; NHANES, National Health and Nutrition Examination Survey; OGTT, Oral Glucose Tolerance Test; OR, Odds Ratio; Perio/PD, Periodontal Disease; PPD, Periodontal Probing (Pocket) Depth; RR, Risk Ratio; Stat. sign., statistically significant; vs., versus; yr(s), Year(s).

study relied on self-report only. The large international study states the participants were representative of people with type 2 diabetes. It used

a non-traditional definition of oral health status, stating that “Lower numbers of natural teeth and higher numbers of days of gum bleeding

indicated poorer oral health,” deducted exclusively from self-report by asking about the participants’ number of teeth present and



Table 3. (continued)

Author			OUTCOME				
Year	A) # Subjects:		Diabetes				
Country	a. Perio Cases	EXPOSURE	Complications:	Effect on	Effect Size:		
Study	b. Comparison group(s)	Perio Measure	Measure	Metabolic	HR, HRR, OR	Effect on Metabolic	
Design	B) Age	&	&	Control?	&	Control/	Confounders
BL DMType	C) Study Duration	Case Definition	Assessment	& Generalisable?	Significance (95%CI)	Conclusion	Controlled
	<u>C) Duration:</u>	loss and <4 teeth w/≥75%			Overall p=0.02		
	C1) Macro-albuminuria:	bone loss					
	9.4yrs [0.03-21.6yrs]						
	C2) End Stage Renal						
	Disease: 14.9yrs [0.03-21.8yrs]						
COMMENTS: Good intra- & inter-examiner calibration agreement for clinical & radiographic examinations (as per personal communication with authors); *Smoking & PD status updated at each examination; **Insignificant in models also adjusted for HbA1c; 72% of extractions due to PD, thus edentulism regarded as most severe form of PD							
Li et al.	A1) N@BL=11,140 (57.5% M+42.5 %F)	<u>Self-report:</u>	• Cardiovascular	Yes, number of	<u># Natural Teeth:</u>	Number of teeth associated	• age
2010		• number of natural teeth	disease	natural teeth in	<u>I) CHD events:</u>	weakly with	• sex
20 countries	A2) N@FU=10,958	• number of days gums bled	• Cerebrovascular	most cases	1) HR=1.24 (0.98-1.56) for 1-	cardiovascular mortality	• randomized
(215 centres)	<u>1) nbvNatural Teeth*:</u>	during previous year	events	associated stat.	21 vs. ≥22 teeth	and cardio- and	treatment allocation
Cohort	a1) 1-21 teeth: 4,174		• Mortality	sign with out-	2) HR=1.04 (0.81-1.23) for 0	cerebrovascular events in	• ethnicity
DM2	a2) 0 teeth: 2,308			comes, but not	vs. ≥22 teeth.	men and women with	• quality of life
	b) ≥22 teeth: 4,476			number of	P=0.34 for trend	DM2	• existing illness
	<u>2) # in Groups by #Days</u>			days	<u>II) Cerebro-vascular events:</u>	Number of days with	• smoking
	<u>w/BleedingGums/1yr:</u>			w/bleeding	1) HR=1.24 (1.03-1.49) for 1-21	bleeding gums/year	• alcohol intake
	a1) <12 days/1yr: 686			gums	vs. ≥22 teeth	weakly and non-	• physical activity
	a2) ≥12 days/1yr: 719			Not generalisable,	2) HR=1.10 (0.87-1.38) for 0	significantly associated	• HbA1c
	b) 0 days/1yr: 9,553			even	vs. ≥22 teeth;	with cardio- &	• creatinine
	B) 65.8(+6.4)yrs[55-88yrs]			though	P=0.29 for trend	cerebrovascular events &	• BMI
	<u>1) Age by Natural Teeth*:</u>			population	<u>III) CVD mortality:</u>	mortality	• total cholesterol
	a1) 1-21 teeth: 6.3(±6.2)			stated to be	1) HR= 1.32 (1.06-1.65) for 1-		• HDL-cholesterol
	a2) 0 teeth: 68.6(±6.4)yrs			represent-	21 vs. ≥22 teeth		• resting heart rate
	b) ≥22 teeth: 63.9(±5.9)			tative of	2) HR=1.35 (1.05-1.74) for 0		• systolic blood
	<u>2) # Days of Bleeding</u>			people with	vs. ≥22 teeth;		pressure (BP)
	<u>Gums/1yr:</u>			type 2 diabetes	P=0.02 for trend		• diastolic BP
	a1) 64.2(±6.0)				<u>IV) # Days of Bleeding</u>		• Mini Mental State
	a2) 63.6(±5.9)				<u>Gums/1Year: Association</u>		Examination score
	b) 66.1(±6.4)				with cerebrovascular		• height
	C) 5yrs				outcomes somewhat weaker		• education
					& statistically non-significant		Multivariate
COMMENTS: Action in Diabetes and Vascular Disease: Preterax and Diami-cron Modified-Release Controlled Evaluation (ADVANCE) study; *Dichotomized values >0 at median to create categories (0, 1-21, ≥22 teeth & 0, <12, ≥12 days); Dose response effect for number of teeth, but not bleeding gums; Inadequate assessment of periodontal condition: Non-validated, non-standard self-report items used; no clinical or radiologic periodontal examination; No knowledge of reason for tooth loss; may not be due to PD; may not be alike in the 20 countries/215 centres							
Abrao et al.	A)N=122 (53M+69F) w/DM2	Partial mouth Exam	Risk for neuro-	Yes, stat. sign.	<u>Edentulous vs. No/Mild:</u>	Periodontal status was	• DM duration
2010	a1) Moderate/Severe:	CPI (ging./BOP/PPD)	pathic foot	Not generalisable	OR=4.9 (1.6- 15.3;	associated with risk for	• education
Brazil	n=39 (32.0%)	<u>PD:</u>	ulceration		p≤0.01)	neuropathic foot ulceration	• age
Cross-sectional	a2) Edentulous:	a1) Moderate/ Severe:			<u>Moderate/ Severe vs. No/Mild:</u>		• dental care
DM2	n=34 (27.8%)	CPI codes 3 or 4			OR=6.6 (2.3-18.8;		
	b) No/Mild:=49 (40.2%)	a2) Edentulous due to			p≤0.001)		Multivariate logistic
	B) 60.5(±10.5)yrs	PD					regression
	[27.9-80.6yrs]	b) No/Mild: CPI= 0, 1, 2					
	C) n/a (cross-sectional)						
COMMENTS: Not controlled for metabolic control, Mean DM duration= 14.5(+9.6)yrs [1-40yrs], Mean HbA1c=9.3(± 2.2)% [4.9-14.7%]							

Table 3. (continued)

Author			OUTCOME				
Year	A) # Subjects:		Diabetes				
Country	a. Perio Cases	EXPOSURE	Complications:	Effect on	Effect Size:		
Study	b. Comparison group(s)	Perio Measure	Measure	Metabolic	HR, HRR, OR	Effect on Metabolic	
Design	B) Age	&	&	Control?	&	Control/	Confounders
BL DMType	C) Study Duration	Case Definition	Assessment	& Generalisable?	Significance (95%CI)	Conclusion	Controlled
Southerland et al. 2012	A) <u>N=6,048</u> n1=791 w/DM2	Full mouth (6 sites/tooth)	• Carotid IMT	Yes, stat. sign.	<u>I) Severe PD assoc. with:</u>	1) Severe periodontal disease was associated	• age
USA	n2=5,257 w/o DM	• PPD	• Calcification of	Not generalisable	1) IMT>1mm: OR=1.3(1.0-1.7)	with subclinical heart disease** in all subjects	• sex
Cross-sectional	B) [52-74yrs]	• CAL	athero-sclerotic plaque		2) Acoustic shadowing: OR=1.3 (1.0-1.9)	(± DM)	• BMI
DM2*	C) n/a (cross-sectional)	<u>extent of PD (&gt;4mm &amp; CAL &gt;3 mm);</u>	• CHD		3) CHD: OR=1.3 (0.9-1.7)	2) Among subjects with type 2 diabetes, periodontal disease was significantly associated	• smoking
		a1) mild/ moderate: 1to<15%			<u>II) Severe PD &amp; DM vs. No PD &amp; No DM asso c. with:</u>	disease** and CHD	• income
		a2) severe: ≥15%			1) IMT>1mm: OR=2.2 (1.4-3.5; p<0.001)		• education
		b) none: 0%			2) Acoustic shadowing: OR=2.5 (1.3-4.6; p<0.001)		• hypertension
		PD & DM status also combined in 6-category variable			3) CHD:OR=2.6 (1.6-4.2;p<0.001)		• LDL cholesterol
							• HDL cholesterol
							• triglycerides
COMMENTS: Dental data from Athero-sclerosis Risk in Communities (ARIC) Study; *DM2 as per personal communication w/authors; Excellent to outstanding inter-examiner calibration agreement for PD; **1) thickened carotid IMT & 2) more advanced atheroma lesions (atherosclerotic plaque calcification measured by acoustic shadowing); Results not controlled for level of glycaemic control							
Noma et al. 2004	A) N =73	X-ray bone loss	Retinopathy	Yes, stat. sign.	PD sign. associated	1) PD sign. assoc. w/ diabetic retinopathy:	None
Japan	B) Age not stated	<u>PD;</u>		Not generalisable	w/diabetic retinopathy: OR=2.80; p=0.036	OR=2.80; P=0.036	
Cross-sectional	C) n/a (cross-sectional)	a) bone loss >median				2) Severity of PD sign. correlated w/severity of diabetic retinopathy (P=0.0012)	
Unspecified		b) bone loss <median					
DM type							
COMMENTS: No examiner calibration reported							

#, Number (of); &, and; Acoustic Shadowing, Advanced atherosclerotic lesions or plaque formation; Assoc., Association/Associated; BL, Baseline/Beginning of Study Period; CAL, Clinical Attachment Loss; CHD, Coronary Heart Disease; CI, Confidence Interval; CPI, Community Periodontal Index; DM, Diabetes Mellitus; DM2, Type 2 Diabetes Mellitus; EKG, Electro Cardiogram; ESRD, End-Stage Renal Disease; F, Female; FU, Follow-Up/End of Study Period; HRR, Hazard Rate Ratio; HbA1c, Glycosylated (Glycated) Haemoglobin; HDL, High-Density Lipoprotein; HR, Hazard Ratio; IMT, Intimal-Medial Thickness; M, Male; MA, Macroalbuminuria; ns, non-significant; OR, Odds Ratio; Perio/PD, periodontal disease; PDP, Pathologically Deepened Pockets; PPD, Periodontal Probing (Pocket) Depth; RR, Risk Ratio; Stat. sign., statistically significant; vs., versus; w/, with; w/o, without; yr(s), Year(s).

“number of days their teeth had bled in the preceding year” (Li et al. 2010). Using the number of teeth as an expression of past periodontal disease may not be appropriate in all these 20 countries, without information on the reason for tooth loss.

All studies regarding type 2 diabetes used multivariate analyses to control for the important confounders displayed in Table 3. Results were statistically significant after adjustment.

As seen in Exhibit Appendix S11, only one study earned the maximum

of nine stars for cohort studies (Saremi et al. 2005). The four longitudinal studies earned between seven and nine stars, averaging eight. None of the three cross-sectional studies were awarded the maximum six stars for studies with such design, but two attained five, and the mean was four stars. The study of the lowest quality was included in this review only for completeness (Li et al. 2010).

#### Major weaknesses

Only one, small study was conducted in type 1 diabetes (Thorstensson et al. 1996). No high quality cohort studies

were conducted in samples representative of individuals with type 2 diabetes. Two of the three cohort studies on type 2 diabetes were conducted in a special population of Pima Indians, and the international study did not use any commonly accepted assessment of periodontal disease. Due to their design, cross-sectional studies can provide information regarding only associations, not causation, and are thus not able to provide strong evidence.

4. Do people without known diabetes, who have poorer periodontal health,

Table 4. Effect of periodontal disease on diabetes incidence (in individuals without diabetes at baseline) (E6)

Author	A) # Subjects:	OUTCOME	Effect on	Diabetes Measure	Metabolic	Effect Size:	Effect on Metabolic	Confounders
Year	b. Comparison	EXPOSURE	Diabetes Measure	&	Control?	HR, OR, RR	Control/	Controlled
Country	group	Perio Measure	&	Definition	&	&	Control/	Controlled
Study Design	B) Age	&	Definition	&	&	&	Control/	Controlled
(No DM@BL)	C) Study Duration	Case Definition	at BL/FU	Generalisable?	Significance (95%CI)	Conclusion	Conclusion	Controlled
Ide et al. 2011	A) # w/oral exams: N=8,752@BL	Partial mouth (sextants)	FPG>125mg/dL @ FU	1) Unadjusted: Yes, in employed 30-59yrs old	1) Unadjusted: HR for trend <0.0001	1) Moderate&severe perio sign. associated w/DM risk (Unadjusted only)	• age	• sex
Japan	/5,848@FU	0: healthy		Japanese	a) No Perio (4.0% DM): HR=1(Referent)	2) Tendency for increased risk, but not sign. after adjustment	• smoking	• BMI
Retrospective Cohort	(3,883M+1,965F)	1: bleeding		2) Adjusted: No	b) Mod.Perio(5.4% DM): HR=1.38(1.08-1.78)	3) Females w/mod. perio. have sign. higher risk for DM	• triglycerides	• hypertension
	Perio: a1) Moderate: 2,167 (37.1%) (1,511M+656F)	2: calculus		Not generalisable	c) Sev.Perio(8.4% DM): HR=2.23(1.57-3.17)		• HDL cholesterol	• gamma-glutamyl-transpeptidase
	a2) Severe:490 (8.4%) (384M+106F)	a1) Mod.: 3			2) Fully Adjusted: Females only: Mod.Perio: HR=2.3(1.30-4.08)			
	b) No:3,191 (54.6%) (1,988M+1,203F)	a2) Sev.: 4						
	B) 30-59yrs; A: FU: M:43.4(±7.5)yrs; F:43.9(±7.5)yrs	b) No: 0, 1, or 2						
	C) 6.5yrs [2-7yrs]							
COMMENTS: 7 "trained" examiners; Intra- & inter-examiner calibration done, but not recorded; Oral exam at BL only; FPG measured 1-6 times 2000-2007; No FU data on n = 2,904 w/oral exam@BL = 33.2% of original study population; No adjustment for education, income, exercise, medication, co-morbidities								
Saito et al. 2004	All without DM @BL in 1988	Partial mouth**	• 2hr 75g OGTT @BL	Yes, stat. sign. in Japanese (Hisayama)	1) High vs. Low PPD categories: Risk of DM:OR=2.6 (1.3-5.0;p=0.004)	1) Proportion w/DM increased significantly w/mean PPD	• age	• sex
Japan	A) @ FU in 1998:	• CAL	• HbA1c	40-79yrs	2) Sign. increase in DM with mean CAL	2) Each additional mm mean PPD corre-sponded to 0.13% HbA1c increase (p=0.007)	• smoking	• BMI
Retrospective Cohort*	N1=961 (377M+584F); N2=591=those among 1988;	PD-1: Mean DDP: a1) Intermediate: 1.3-2.0mm		community dwellers			• exercise	• alcohol
No DM	N1 aged ≥40yrs in 1988;	a2) Deep/High: >2.0mm		Not generalisable				
	N3=545 w/HbA1c values both at BL and FU	b) Shallow/Low: <1.3mm				3) Severity of periodontal disease (expressed as either PPD or CAL) was sign. associated with development of manifest diabetes		
	B) 40-79yrs	PD-2: Mean CAL:						
	C) 10yrs	a1) Intermediate: 1.5-2.5mm						
		a2) High: >2.5mm						
		b) Low: <1.5mm						
COMMENTS: *May be regarded as 1998 cross-sectional exam plus 1988 OGGT data, i.e., oral health data only from 1998 (not from BL 1988); **NHANES III protocol (1 max.+ 1 mand. quadrant) 4 "trained" examiners; No calibration reported								
Denmer et al. 2008	A) N @ BL =11,375 (40%M+60%F)	NHANES I protocol	• death certificates	Yes, stat. sign. in US adults	1) Compared to those periodontally healthy (PI=0), the risk of incident DM were:	1) The extent of periodontal disease (using PD-1) and periodontitis (using PD-2) were associated with incident diabetes	• age	• sex
USA	n @ FU =9,296	• gingival inflammation extent	• DM discharge diagnosis from health care facility	Generalisable to US adults	1a) PD-1 <sup>†</sup> : OR for PI quintiles w/increasing PD: a1) 1.10(0.73-1.64) a2) 1.03(0.65-1.63)	2) The association of periodontal disease (PD-1) and periodontitis (PD-2) with incident diabetes was	• race	• education
Prospective Cohort	PD Groups@BL: PD-1 <sup>†</sup> (PI)=Periodontal Index: a1) 762 (>0-0.87) a2) 761 (0.88-1.60) a3) 759 (1.61-2.44)	• presence or absence of periodontal pockets	• self-reported DM requiring medication				• smoking status	• BMI
		• tooth mobility					• subscapular skinfold	• physical activity
		PDGroups@BL: PD-1 <sup>†</sup> (PI): "Periodontal Index"					• hypertension	

Table 4. (continued)

Author	A) # Subjects:	OUTCOME	Effect on	Diabetes Measure	Metabolic	Effect Size:	Control/	Confounders
Year	b. Comparison	EXPOSURE	&	&	&	HR, OR, RR	&	Controlled
Country	group	Perio Measure	&	&	&	HR, OR, RR	Effect on Metabolic	
Study Design	B) Age	&	Definition	&	&	&	Control/	Confounders
(No DM@BL)	C) Study Duration	Case Definition	at BL/FU	Generalisable?	Significance (95%CI)	Conclusion	Conclusion	Controlled
	a4) 759 (2.45-5.07)	(Mean Score(0-8)			a3) 2.08(1.51-2.87)	found also in normo-weight		• total cholesterol
	a5) 760 (5.08-8.0)	for Dentition):			a4) 1.71(1.19-2.45)	andin never-smoking		• total caloric intake
	a6) 2,127edentulous	a1) lowest PI to			a5) 1.50(0.98–2.27)	participants		• total protein
	b) 3,368 (PI=0)	a5) highest PI quintile			1b) <u>PD-2<sup>86</sup></u> .			• total carbohydrate
	(healthy)	a6) edentulous			Those with gingivitis had			• total fat
	<u>PD-2<sup>86</sup></u> :	b) healthy: PI=0			40% and those with			• poverty index
	a1) 2,135 gingivitis	<u>PD-2<sup>86</sup></u> :			periodontitis 50% increased			• white blood cell count
	a2) 1,662 perio	a1) 2,135 gingivitis			odds of developing DM			
	b) 3,372 healthy	a2) 1,662 perio			(p< 0.05 for both)			
	B) 50±19yrs	b) 3,372 healthy			1c) <u>Edentulous</u> :			
	[25-74yrs]	<u>PD-3</u> :			OR=1.3(1.00-1.70)			
	C) 17(±4)yrs	# Natural Teeth:			2) <u>PD-3</u> : Dentate with			
	[1-22yrs]	a1) 18-23			advanced tooth loss (25-31			
		a2) 8-17			teeth missing) had			
		a3) 1-7			OR=1.70 (P<0.05) relative			
		b) 24-32			to those with minimal tooth			
					loss (0-8 teeth)			
COMMENTS: Data from NHANES 1 [1971-1976 (BL)] & NHEFS 1982-1992 (FU); n = 817 incident DM cases were reported (cumulative incidence = 9%); & Wu et al. 2000; #) Hujuel et al. 2000								
Morita et al.	A) # @ BL unknown*	Partial mouth	• HbA1c≥6.5% @	Yes, stat. sign.	Relative risk (RR) for	Periodontal disease (pockets		• BMI
2012	N @ FU=6,125	CPI	FU	in employed	HbA1c≥6.5% at 5yr FU in	≥6mm) leads to increased		• alcohol
Japan	(76.6%M+23.4%F)	<u>CPI Code 0</u> :		30-69 years old	groups w/PPD of 4-5mm	inci-dence of type 2		• smoking status
Cohort	w/BL HbA1c<6.5%	Healthy gingiva		(76.6% male)	was 2.47 (0.78-7.79);	diabetes (HbA1c>6.5%) in		• sex
	<u>Nby CPI Code:</u>	<u>CPI Code 3</u> :		Japanese	p=0.122) and for those	5 years		• age
	a1) 4,114	≥1 PPD= 4-5mm		(Nagoya)	w/PPD of ≥6mm: 3.45			
	(3,383M+731F)	<u>CPI Code 4</u> :		Not generalisable	(1.08-11.02; p=0.037)			
	a2) 1,634	≥1 PPD> 6mm						
	(1,424M+210F)	<u>PD by CPI Code</u> :						
	b) 377 (240M+137F)	a1) 3						
	B) [30-69yrs]	a2) 4						
	C) 4-5.5yrs	b) 0						
COMMENTS: *No FU of those who left the workplace during study period; Kappa statistics 0.7-0.9 for calibration of 7 dentist periodontal examiners; Dose-response effect % of BL CPI codes 0, 3, & 4 w/5yr HbA1c>6.5%: 0.8%, 2.5%, and 3.9% (p = 0.001)								

#, Number (of); &, and; BL, Baseline/Beginning of Study Period; CAL, Clinical Attachment Loss; CI, Confidence Interval; CPI, Community Periodontal Index; DM, Diabetes Mellitus; F, Female; FPG, Fasting Plasma Glucose; FU, Follow-Up/End of Study Period; HbA1c, Glycosylated(Glycated) Haemoglobin; HDL, High-Density Lipoprotein; hr, hour; HR, Hazard Ratio; M, Male; Mod. , Moderate; NHANES 1, First National Health and Nutrition Examination Survey; NHEFS, NHANES 1 epidemiologic Follow-up Survey; OGTT, Oral Glucose Tolerance Test; OR, Odds Ratio; Perio/PD, Periodontal Disease/Periodontal/Periodontally; PPD, Periodontal Probing (Pocket) Depth; RR, Risk Ratio; Sev., Severe; Stat. sign., Statistically Significant; vs., Versus; w/o, Without; yr(s), Year(s).

have greater risk for developing (incident) type 2 diabetes than those with better periodontal health? (E6)

**Brief summary of characteristics and results**

Three of the four eligible studies displayed in Table 4 were conducted in

Japan and one in the USA. Numbers of participants at the end of the studies were 12,934 in the former three and 9296 in the latter, totalling 22,230 individuals. The two largest Japanese studies included employed adults aged 30–59 and 30–69, respectively, and the third was community

based among 40–79 year olds. Demmer et al. analysed data representative of the US population between 25 and 74 years of age (Demmer et al. 2008).

During study periods of 1–22 years, three of the four studies demonstrated a statistically signifi-

cant increase in development of manifest diabetes in people with severe periodontal disease, determined by periodontal probing depth, after adjustment for potential confounders (Saito et al. 2004, Demmer et al. 2008, Morita et al. 2012). In the fourth, the tendency for increased risk was not significant upon adjustment, except in Japanese employed females with moderate periodontal disease (Ide et al. 2011).

For instance, those with PPD of 6 mm or greater at baseline had 3.45 times higher risk of developing diabetes than those without periodontal disease (Morita et al. 2012). In the US population, people with gingivitis had 40% increased odds of developing diabetes and those with periodontitis had 50% elevated risk. In edentulous individuals, the risk was increased by 30 per cent and those with advanced, but not complete, tooth loss had a 70 per cent increased risk of incident type 2 diabetes. Measured by two different indices, the association of periodontal disease with incident diabetes was found also in individuals who were of normal weight as well as among people who had never smoked cigarettes (Demmer et al. 2008).

In addition, severity of periodontal disease expressed by clinical attachment loss at follow-up was significantly associated with development of diabetes over ten years in the smallest study (Saito et al. 2004), in which each additional millimetre mean PPD corresponded to 0.13% HbA1c increase ( $p = 0.007$ ).

#### *Quality assessment*

The generally high quality of this group of large, longitudinal studies is reflected in the high NOS star ratings as displayed in Exhibit Appendix S12, with two earning the maximum of nine stars, one-eight and one-seven, averaging 8.3.

#### *Major weaknesses*

Eligible studies were performed exclusively in Japan and the United States with only one smaller Japanese (Saito et al. 2004) and the large US (Demmer et al. 2008) studies being representative of the general population. Two were conducted in Japan among employees (Ide et al. 2011, Morita et al.

2012). Major concerns regarding the Japanese work place studies were, *firstly*: The oral health examinations were not conducted for research and used the Community Periodontal index (CPI) (Ainamo et al. 1982), a quick periodontal assessment of ten index teeth that does not adequately represent the periodontal health status. *Secondly*, employees who left the company during the study period were not re-examined at the end. In one study, it remains unknown how many were lost to follow-up (Morita et al. 2012); and in the other, a total of 2904 or one-third (33.2%) of the employees who received oral exams at baseline were not re-examined at the end of the study (Ide et al. 2011). Such unknown and large attrition, respectively, does not lead to confidence that those remaining in the study were representative of those originally examined. *Thirdly*, the employees included two to three times more males than females, and the analyses were not adjusted for education level that could be different in the two sexes. The Japanese community-based study included an oral examination only at follow-up and therefore did not provide any knowledge of the periodontal status at baseline (Saito et al. 2004). This study could be regarded as a cross-sectional examination, supplemented with additional oral glucose tolerance test (OGTT) data from ten years earlier. Even though the results from the three Japanese studies were significant, this evidence may not be transferable to other race/ethnic groups since differences in fat storage and other factors may be operative. The national US study used periodontal inflammation, PPD and number of teeth present to evaluate the periodontal health status, whereas CAL was not assessed.

*5. Do women with gestational diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health? (E4)*

AND

*6. Do pregnant women, who have poorer periodontal health, have greater risk for gestational diabetes*

*than those with better periodontal health? (E5)*

#### *Brief summary of characteristics and results*

Shown in Table 5 are the only two eligible small American case-control studies that examined the effect of periodontal disease on prevalence of gestational diabetes (GDM). One demonstrated that GDM in a dose-response manner consistently was associated with clinical PD using three different PD definitions (Xiong et al. 2009). The other concluded that having sites with periodontal probing depths of 3 mm or greater was not associated with GDM, although high vaginal levels of the periodontal pathogen, *Tannerella forsythia*, was associated with gestational diabetes (Dasanayake et al. 2008).

#### *Quality assessment*

One study used full-mouth periodontal probing, applied three PD definitions, and controlled for several potential confounders (Xiong et al. 2009), whereas the other defined PD as having at least one site with PPD of 3 mm or greater and controlled for only history of GDM. In pregnant women, PPD of 3 mm could represent non-pathological conditions, namely increased probing depths due to hormonal changes and oedema. Exhibit Appendix S13 displays the consensus ratings regarding the quality of these two studies.

#### *Major weaknesses*

There were only two studies, and they were small, of case-control design, and conducted among non-representative samples, making their findings non-generalizable.

## **Discussion**

### **Summary of the evidence**

Current evidence for effects of periodontal disease on glycaemic control is scarce. However, it suggests that compared to periodontally healthy individuals, people with poor periodontal health and:

- *type 2 diabetes or no diabetes:* have greater risk of developing poorer glycaemic control

Table 5. Effect of periodontal disease on gestational diabetes (E4/E5)

A) # Subjects:							
a. Gestational							
Author	Diabetes Cases	OUTCOME					
Year	(GDM)	EXPOSURE	Gestational Diabetes	Effect on	Effect Size:		
Country	b. Comparison	Perio Measure	Measure	Metabolic	OR	Effect on Gestational	
Study Design	group	&	&	Control?	&	Diabetes	
(All GDM)	B) Age	Case Definition	Definition	& Generalisable?	Significance (95%CI)	Conclusion	Confounders Controlled
Xiong et al. 2009	A) N=159 pregnant: a. 53 GDM	Full mouth exam (6 sites/tooth)	• 50g oral glucose challenge test (GCT)	Yes, stat.sign. for most exposure	OR for GDM: • PD (PPD ≥4mm or CAL≥4mm) vs. perio- dontally healthy: OR=2.6 (1.1-6.1; p=0.014)	1) Periodontitis was consistently associated with increased risk of GDM, regardless of PD definition	• maternal age • parity
USA	b. 106 non-GDM	• ging/BOP	• 100g OGTT	parameters			• race
Case-Control	B) Age (Mean±SD):	• PPD	b. Comparison group:	Not generalisable			• marital status
GDM	a. 29.9(±5.6) yrs	• CAL	• Passed 50g GCT				• education
	b. 27.1(±5.9) yrs	• gingival recession	• No DM of any type			2) There was a dose- response relationship of increased GDM risk with increasing severity of periodontal di-sease, assessed by PPD or CAL	• income • family income • smoking • alcohol • systemic antibiotics in pregnancy • family DM history • dental insurance • BMI Multivariate
<p>PD1: ≥1 PPD ≥4mm or ≥1 CAL ≥4mm</p> <p>PD2&amp;3: 2 additional PD definitions used Extent measured by PPD &amp; CAL</p>							
<p>COMMENTS: Intra- &amp; inter-examiner calibration reported; but only 1 dental examiner; PD extent (PPD, CAL) used as continuous &amp; categorical variables; Dose-response effect stat. sign. for trend; PD (≥1 PPD ≥4 mm or ≥1 CAL ≥4 mm) in 77.4% of GDM vs. 57.5% without GDM: OR = 2.5 (1.2-5.3; p &lt; 0.05)</p>							
Dasanayake et al. 2008	A1) N @ BL=268*	1) 5 Periodontal Patho- gens** from:	GDM	Yes:Vaginal <i>Tannerella</i>	1) Elevated risk for GDM in women with high vaginal levels of <i>Tannerella</i> <i>forsythia</i> had a stat. sign. effect on GDM	1) Levels of <i>Tannerella</i> <i>forsythia</i> in the vagina, but not in the cervix or in dental plaque, emerged as a risk factor for GDM	• Prior GDM
USA	A2) N @ FU=265 pregnant:	• dental plaque	OGTT: 1hr, 2hrs, or 3hrs				
Case-Control	a. 22 GDM	• cervix					
GDM	b. 243 non-GDM	• vagina					
	B) a. 28.7(±5.3) yrs	2) Clinical PD:		Not generalisable	2) <i>T. forsythia</i> in cervix (OR=1.04; 0.85-1.28)	2) Having one or more sites with periodontal probing depth of 3mm or more was not a risk factor for GDM	
	b. 26.6 (±5.8) yrs	Partial mouth					
		• PPD					
		• BOP					
		PD:					
		≥1 PPD≥3mm			3) Having PD (OR=1.68; 0.52-5.43): not stat. sign.		
<p>COMMENTS: *83% Hispanic Examiner calibration not reported; **Clinical, bacteriological, immunological, and inflammatory mediator parameters assessed 7 weeks prior to diagnosis of GDM; Prevalence of ≥1 PPD ≥3 mm: 50% in GDM vs. 37% in non-GDM; difference not stat. sign. (p = 0.38)</p>							

#, Number (of); &, and; BL, Baseline/Beginning of Study Period; BOP, Bleeding On Probing; CAL, Clinical Attachment Loss; CI, Confidence Interval; DM, Diabetes Mellitus; FU, Follow-Up/End of Study Period; GCT, Glucose Challenge Test; GDM, Gestational Diabetes Mellitus; Ging., Gingival; hr(s), Hour(s); HR, Hazard Ratio; OGTT, Oral Glucose Tolerance Test; OR, Odds Ratio; Perio/PD, Periodontal Disease, Periodontal/Periodontally; PPD, Periodontal Probing (Pocket) Depth; RR, Risk Ratio; Stat. sign., Statistically Significant; *T. forsythia*, *Tannerella forsythia*; vs., Versus; yr(s), Year(s).

- type 1 or type 2 diabetes: have greater risk for diabetes-related complications

- no diabetes: have greater risk of developing manifest diabetes.

Results of only two studies exploring the effect of periodontal disease on gestational diabetes are inconclusive.

## Limitations

### Study and outcome level

Only 17 reports were eligible for inclusion in the final review and included only one study on type 1 and two on gestational diabetes. Most studies were small, except those exploring diabetes incidence. The studies were conducted in a limited number of countries. A major limitation in all studies regarding periodontal disease is the lack of generally accepted case definitions for periodontal disease, which severely impedes or prevents comparison of studies (Tonetti & Claffey 2005, Page & Eke 2007, Manau et al. 2008, Costa et al. 2009, Leroy et al. 2010). Because both diabetes and periodontal disease are multifactorial, chronic diseases, most studies were not sufficiently extensive in size, duration and number or kinds of parameters to control for all potentially important confounders.

### Review level

To maximize comprehension and interpretation of the findings, only reports published in the English language were included, which may have excluded potentially valuable evidence. Moreover, we may have overlooked evidence in English that we failed to identify, but we succeeded in retrieving all but one full text article that, based on the abstract, probably was a cross-sectional study, and thus ineligible for inclusion. As with any scientific evidence, publication bias resulting from a tendency to preferentially publish positive study findings may have played a role in creating the pool of published reports.

## Conclusion

Scant current evidence suggests that periodontal disease adversely affects glycaemic control and diabetes complications or promotes development of type 2 diabetes. Consequently, large-scale, definitive studies of long duration and in multiple different population groups in many different countries are needed in all the areas this review explored.

### Consequences

Should it be possible to demonstrate an adverse effect of periodontal dis-

ease on glycaemic control, with periodontal disease being a risk factor for diabetes complications and incident diabetes, such evidence could have far-reaching consequences. Impacted would be patients and families, health care providers, insurance companies, policy-makers and societies in general, due to the high prevalence of both periodontal disease and diabetes that incurs immense societal, economic consequences and human suffering. Controlling and managing periodontal disease may be a new alternative to eventually include in standards for diabetes care. Such shift in paradigm for management and prevention of diabetes and its complications may occur in the future.

While waiting for definitive evidence, it may be wise to make efforts to prevent – and treat to resolution any existing – periodontal disease, in order to ensure good health.

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### Supporting Information

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

**Appendix S1.** Overview: Databases Searched for Evidence.

**Appendix S2.** Scoring Form: Recording Ineligible Studies and Reasons.

**Appendix S3.** Overview: The 97 Reports Excluded Based on Full Text: Citations and Main Exclusion Reason.

**Appendix S4.** Scoring Form: Description and Findings (All Study Designs).

**Appendix S5.** Overview: The 16 Reports (17 Studies) Included in the Final Review: Eligibility Category & Citation.

**Appendix S6.** Description of the Newcastle-Ottawa Scale (NOS) for Quality Rating.

**Appendix S7.** Scoring Form: Quality of a Cohort Study.

**Appendix S8.** Scoring Form: Quality of a Case-Control Study.

**Appendix S9.** Scoring Form: Quality of a Cross-sectional Study.

**Appendix S10.** Consensus Quality Rating: 4 Studies on Effect of Periodontal Disease in Type 2 Diabetes (E1a) and No Diabetes (E1c).

**Appendix S11.** Consensus Quality Rating: Studies on Effect of Periodontal Disease on Diabetes Complications (E3).

**Appendix S12.** Consensus Quality Rating: Studies on Effect of Periodontal Disease on Incidence of Diabetes Mellitus (E6).

**Appendix S13.** Consensus Quality Rating: Studies on Effect of Periodontal Disease on Gestational Diabetes (E4/E5).

Address:

*Wenche S. Borgnakke*

*School of Dentistry*

*University of Michigan*

*1011 North University Avenue Rm#G049*

*Ann Arbor MI 48109-1078 USA*

E-mail: [wsb@umich.edu](mailto:wsb@umich.edu)

### Clinical Relevance

*Scientific rationale for the study:* Periodontal disease and diabetes mellitus are common chronic diseases occurring worldwide. This systematic review explored the epidemiologic, non-experimental, observational evidence for effects of periodontal disease on diabetes.

*Principal findings:* Poor periodontal health is associated with worsening of glycaemic control and complications in diabetes, as well as development of type 2 diabetes.

*Practical implications:* The current, limited evidence suggests that periodontal disease negatively influences diabetes outcomes, and that further

longitudinal studies are warranted. In the meantime, dental care professionals should prevent or definitively treat periodontal disease, especially among patients with diabetes.