The risk of tooth loss in patients with diabetes: 

* a systematic review and meta-analysis

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Abstract

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

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

Results
A total of 1,087 references were generated, and independent screening of the papers resulted in 10 eligible publications. A descriptive analysis demonstrated that six of these studies indicate a significantly higher risk of tooth loss in DM patients. This was confirmed by the meta-analysis risk ratio of 1.63 (95%CI: 1.00, p < 0.00001).
Subgroup analysis illustrates that this is irrespective of the risk of bias assessment. The higher risk of tooth loss in DM patients was also higher when only DM type II patients or studies with a cross-sectional design were considered. Patients with a poor DM control status presented a significantly increased risk of tooth loss. When the data were separated by the world continent where the study was performed, Asia and South America had numerically higher risks and a 95%CI that did not overlap with Europe and North America.

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

Scientific rationale for the study:
Diabetes Mellitus (DM) is a chronic inflammatory disease. Evidence supports an increased risk for periodontal diseases and incidence/severity of caries in DM patients. Both are primary sources of tooth loss. It has not been systematically being reviewed whether DM is associated with a higher risk of tooth loss compared to non-DM individuals.

Principal findings:
DM patients have a significantly higher risk of tooth loss than in non-DM individuals.

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

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

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

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

The preparation and presentation of this SR is in accordance with the Cochrane Handbook for Systematic Reviews\textsuperscript{17} and the guideline for Meta-Analysis of Observational Studies in Epidemiology (MOOSE).\textsuperscript{18}

A protocol was developed a priori following the initial discussion between the members of the research team. This study is registered at the ACTA University Ethical Committee by number 2021-71228.

2.1 Focused question

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

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

2.2 Search strategy

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

PLEASE INSERT TABLE 1 HERE

The reference lists of the studies included in this review were hand-searched to identify additional potentially relevant studies. Moreover, national (http://wwwtrialregister.nl) and international trial registries (http://apps.who.int/trialsearch, http://www.ClinicalTrials.gov) were searched for relevant unpublished or ongoing studies. Furthermore, the following database sources were searched for possible relevant studies that have not reached full publications: OpenGrey (http://www.opengrey.eu/), British Library Inside (http://www.bl.uk/inside), the European Federation of Periodontology (http://www.epf.net), the International Association for Dental Research (http://www.iadr.org), Web of Science, BIOSIS Previews and OVID (http://www.ovid.com).

The conference proceedings of the International Association for Dental Research and the European Organization for Caries Research were searched through October 2020. Additionally, the previous 12 months of the following journals were hand-searched to eliminate potential delay in indexing journals at the
2.3 Screening and selection

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

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

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

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

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

- Full-text paper available in English.
- Observational studies: cohort, case-controlled or cross-sectional studies. Data should be presented as a cross-sectional design.
- Studies conducted with human subjects who were:
  - ≥ 18 years.
  - In satisfactory general health (no systemic disorders or comorbidities).
  - Evaluating a group of patients with DM as well as a group of people without DM.
- DM status:
  - Either self-reported or clinically assessed.
  - Type of DM: undefined, type I and/or type II. Prediabetes and gestational diabetes were excluded.
- Reported outcomes:
  - Based on a full-mouth assessment.
  -Clinically determined number of teeth (no radiographs).
  -Number of missing teeth or number of teeth present as an absolute number of teeth or as a population mean.
  -Tooth loss presented as cross-sectional data for an individual over the lifetime until the moment of assessment (not for the duration of a specific period).

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

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

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

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

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

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

2.5 Data extraction

For those papers that provided insufficient data to be included in the analysis, the first or corresponding authors were contacted by email to query whether additional data could be provided.

Independent data extraction was performed by two reviewers (L.P.M.W. and D.E.S.) utilizing a custom-designed standardized data extraction form. Disagreement between the reviewers was resolved through discussion and consensus. If disagreement persisted, a third reviewer (G.A.W.) was consulted; this judgment was decisive. Data extraction of all included studies having either an observational, cohort or case-controlled design were approached as cross-sectional studies. From the eligible papers, details on study design, demographics, details of the DM status and number of missing teeth or teeth present was extracted. The latter was determined by utilizing the following parameters:

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

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

2.6 Data analysis

2.6.1 Assessment of clinical and methodological heterogeneity

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

- Characteristics of participants: age, gender and continent
Factors employed to assess the methodological heterogeneity were study design details and the total number of evaluated teeth, reference point (28 or 32).

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

As the total number of evaluable teeth (28 or 32) has a direct influence on the relative ratio of the missing teeth to the total number of teeth, this was defined a priori as a reason for subgroup analysis. Other potentially relevant subgroup analyses were study design (studies originally designed as cross-sectional evaluations), participant demographics, potential risk of bias and the world continent where the study was performed and data were obtained. For DM-related details, a sub-analysis was also conducted with respect to DM control (poor or well regulated), insulin dependence (yes or no), and DM duration.

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

2.6.3 Quantitative methods
A meta-analysis was performed comparing the number of missing teeth among patients with DM to those without DM. For a subsequent subgroup analysis, a meta-analysis was performed if more than one study could be included. Analysis was performed utilizing Review Manager version 5.324 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and MOOSE guidelines25,18 as well as the Cochrane handbook.17 From the data, the relative risk or risk ratio (RR) with its associated 95% confidence interval and p-value were calculated for the number of missing teeth among DM patients as compared to non-DM individuals. P-values \( \leq 0.05 \) were considered to be significant.

The absolute number of teeth per group in a study were utilized so that the data were weighed according to the study population. If the absolute numbers were not provided, then the number of teeth for the entire group was calculated based on the population mean multiplied by the number of participants in each group (DM or non-DM).

The RR between DM patients and non-DM individuals was calculated utilizing both a random and fixed-effects model where appropriate. When there was heterogeneity that could not readily be explained, the analytical approach was conducted according to a random-effects model. If there were less than four studies, then a fixed-effects analysis was performed because it may be impossible to estimate the between-study variance with any precision. In such a case, the fixed-effects model is the only option.17
It was expected that there would be considerable heterogeneity among the included studies, as study designs and details presumably differ. Moreover, DM is not likely to be the single cause for tooth loss. Clinically, DM can vary in its features, which is likely and was the case in the DM population of the included studies. This variance was considered by primarily utilizing the random-effects model, the exception being when less than four studies were eligible for meta-analysis. Otherwise, the fixed-effects model was utilized, as advised by the Cochrane Oral health group. Sensitivity analyses were undertaken to evaluate the effect of excluding studies based on specific aspects in the domain of clinical or methodological heterogeneity. The testing for publication bias per outcome was utilized as proposed by Egger et al. If the meta-analysis involved a sufficient number of trials to make visual inspection of the funnel plot meaningful (a minimum of 10 trials), then these plots were employed as tools to assess publication bias. The presence of asymmetry in the inverted funnel is suggestive of publication bias.

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

2.7 Grading the body of evidence
Two reviewers (L.P.M.W. and D.E.S.) rated the quality of the evidence and the strength of the recommendations according to the following aspects: study limitations, inconsistency of results, indirectness of evidence, imprecision and publication bias by utilizing the Grading of Recommendations Assessment, Development and Evaluation (GRADE) which provides a systematic approach for considering and reporting each of these factors. An overall rating of confidence in effect estimates was considered critical for the final recommendation. Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, then the judgment of a third reviewer (G.A.W.) was decisive.
3. Results

3.1 Search and selection process
Searching the MEDLINE-PubMed and Cochrane databases resulted in 1,087 unique papers, as Figure 1 illustrates.

PLEASE INSERT FIGURE 1 HERE

The first screening of the titles and abstracts resulted in 27 papers for which the full papers were obtained. In the second phase, after full-text reading and contact with the corresponding authors, 16 studies were excluded for which reasons are presented in online appendix S1. Three papers do not provide necessary data regarding the overall number of missing teeth, and after contacting the authors, this information could not be retrieved (Wiener et al. 201733, Kapp et al. 200734, Jung et al. 2010).35 Oliver and Tervonen(1993)36 performed only half-mouth assessments. Three papers that present the number of missing teeth over a period of time were not included(Yoo et al. 201937, Mayard-Pons et al.201538 and Jimenez et al.2012).39 Other reasons for exclusion are found in the table in the online Appendix S1. Hand-searching of the reference list did not reveal any additional papers. Consequently, 11 papers were identified which presented 10 different studies, as data from the paper of Costa et al.(2013)40 and Costa et al.(2011)41 concern the same study population.

PLEASE INSERT TABLE 2 HERE

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

One case-control study makes an effort to match the gender distribution(III). The population in Study II is a specific ethnic group (Hispanics or Latinos). Studies originating from the following world continents are present: Europe(VII,IX and X), North America(II,IV, and VIII), Asia(II and VI) and South America(III and V).50 All studies include a non-DM group in satisfactory general health who were drawn from the population of the country where the study was performed. The DM participants in Studies IX and X were specifically selected from a central hospital or institute for metabolic diseases. For inclusion in the individual studies, criteria and diagnoses were utilized regarding DM status: self-reported(IV) and clinically assessed DM(II,III,IV,VII,IX and X).45 The clinical assessments were performed by different methods, such as fasting plasma glucose(FPG), glucose or HbA1c levels. Study VII reports DM based on
both clinical assessments and self-reports. In one paper, it was unclear how the DM status had been assessed (X).46

In total, three studies specifically focus on DM type II (I42, III40 and VIII).48 One paper differentiates between types I and II (VII).44 For the overall calculations, data from these groups were merged, while for the subgroup analysis, the original group data was employed. Originally, Study VIII48 made this distinction, but as the type I DM group included children, this group was consequently excluded from data extraction and only the data on type II DM patients were utilized. Two studies (II43 and III40) report data on the DM group about well- and poorly controlled individuals. Smokers among non-DM individuals were separately analyzed in Study V50, and as none of the DM patients reported smoking, only the non-smoking, non-DM individuals were considered as a control group. Other characteristics concerning DM include short or long duration of DM (X46), insulin independence (IX45) and diagnosis of DM known beforehand or assessed on the spot.

3.3 Assessment of methodological heterogeneity

Eight of the included observational studies utilize a cross-sectional design (I42, IV47, V50, VI48, VII44, VIII48, IX45 and X46), one is a prospective cohort (II43), and one is a retrospective case-control (III).40 Two included papers employ data from national databases: NHANES, KNHANES (I42 and IV47), two papers utilize data from a national study: NFBC-1966, SHIP and HCHS/SOL (VII44 and II).43 Study II40 includes patients who were enrolled in a periodontal maintenance program. The number of evaluated teeth is 32 in two studies (VI49 and IX45) and 28 in eight studies (I42, II43, III40, IV47, V50, VII44, VIII48 and X).46

3.4 Methodological quality assessment

A summary of the methodological quality and potential risk of bias scores is presented in Table 3. Detailed quality assessment for each included study is provided in the online Appendix S2.

PLEASE INSERT TABLE 3 HERE

Based on a summary of the bias assessment domains, the estimated potential risk of bias is low for two studies: II43 and VII44; moderate for the majority of the studies: I42, III40, V50, VIII48 and X46 and serious for the remaining three studies: IV47, V49 and IX.45

3.5 Study results

From the included studies, the overall DM population consisted of 5.699 patients and the non-DM controls of 23.579 individuals. The overall prevalence of DM in the included cross-sectional studies is 16.8%.
Description of findings
Table 4 describes and summarizes the statistical differences as reported in the original studies between DM patients and non-DM individuals with regard to the number of missing teeth.

PLEASE INSERT TABLE 4 HERE

From the 10 overall comparisons, six provide data and indicate significantly more tooth loss for the DM patients. Four of the included studies do not specify or are unclear whether any statistical differences between the DM and non-DM controls were present.

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

PLEASE INSERT FIGURE 2 HERE

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

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

A subgroup analysis on the world continent in which the study was performed resulted in a RR for Europe of 1.39 at a 95%CI(1.35;1.42,p<0.0001), North America 1.22 at a 95%CI(1.20;1.24,p<0.00001), Asia 2.30 at a 95%CI(2.25;2.36,p<0.00001) and South America 2.27 at a 95%CI(2.00;2.58,p<0.00001). For all continents, the risk for tooth loss in DM patients was higher as compared to non-DM individuals (for details, see online Appendix S3.3).
Only Study VII[44] presents usable data for a DM type I group, and therefore, no specific subgroup analysis could be performed. For the studies that solely evaluate DM type II, the RR for tooth loss was 1.56 at a 95%CI(1.02;2.39,p=0.04; for details, see online Appendix S3.4).

Furthermore, a subgroup analysis on DM status was performed. No significant difference was found regarding tooth loss when well-controlled DM patients were compared to non-DM individuals, as demonstrated by the RR: 1.03 with a 95%CI of 1.00 to 1.06(p=0.04). A higher risk of tooth loss in poorly controlled DM patients was found when compared to non-DM individuals (RR=1.25 with a 95%CI of 1.22 to 1.29(p<0.00001) and also when compared to well-controlled DM patients (RR=1.21 with a 95%CI of 1.17 to 1.26(p<0.00001); for details, see online Appendix S3.5.

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

Statistical heterogeneity

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

Publication bias

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

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

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4. Discussion

The present review summarizes the available body of dental and medical literature with respect to an important question that examines the association between DM and tooth loss. The results of this study indicate a higher probability (RR=1.63) of tooth loss for patients with DM as compared to non-DM individuals. This appears to align with what is reported in other epidemiologic studies, as several have supported the link between DM, periodontal diseases and dental caries. These are the two most common reasons for the endpoint parameter of tooth loss.

Selection choices made

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

With this approach, it was considered that the most reliable and valid estimation of the RR was obtained.

Diabetes Mellitus comorbidities

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

**Reporting Bias**

The main origin of publication bias is failure to publish negative outcomes or null findings. Additionally, it is more difficult to publish papers in which no differences between groups are found.\(^{29,62}\) The consequences are that this may lead to overestimation of exposure as deducted based on the meta-analyses.\(^{63}\) The present funnel plot (see online Appendix S4) illustrates that almost all outcomes were located at the top of the funnel, suggesting that relatively few small studies were included. The usage of a strict inclusion criteria may explain this specific distribution. It is recognized that studies with small sample sizes that fail to establish a difference between groups have either not been published or have difficulties in being published in impact factor journals.\(^{62}\)

**Type of Diabetes**

As prediabetes may be reversible\(^{64}\), data from these participants were not considered, as only one study\(^{43}\) was available. Gestational diabetes consists of high blood glucose only during pregnancy\(^{66}\) and was consequently not analyzed in the present review. Type I diabetes can develop at any age but occurs most frequently in children and adolescents. However, type II DM, is more common in adults and accounts for approximately 90% of all diabetes cases.\(^ {65}\) Three of the included studies specifically focus on DM type II\(^ {1,40,48}\) and VIII\(^ {48}\). Only one paper\(^ {44}\) differentiates between types I and II. It was therefore not possible to perform a subgroup analysis to compare types I and II in this dataset. Analysis focused on DM type II, for which a RR of 1.56 for the risk of tooth loss was found. However, the relationship between DM type II and tooth loss is complicated by the fact that the disease onset generally occurs in middle and late ages, coinciding with the time that periodontitis becomes more prevalent.\(^ {44}\) Nevertheless, studies focusing on type I DM patients also indicate an increased risk of periodontitis compared to non-DM individuals. Study VIII\(^ {48}\) includes children, and this group was consequently excluded because children can have temporary, mixed or permanent dentition.

Considerable heterogeneity was observed in the outcomes of most sub-analyses; however, sub-analysis on diabetes type II did not provide an explanation for the high level of heterogeneity. Only the subgroup analysis on diabetic status being either poorly or well controlled revealed a low level of statistical heterogeneity\((0–23\%)\). This could indicate that diabetic control is an aspect that contributes to heterogeneity among study outcomes. However, this sub-analysis was based on only two studies that had similar populations and study designs. Because this study’s meta-analyses indicated a heterogeneity in the outcome, the reader should exercise caution in utilizing the RR as the exact measure of the risk for tooth loss.
**Type of assessment**
The Centers for Disease Control and Prevention have estimated that among US individuals, DM is underdiagnosed, which implies that participants in the included studies may have been unaware of their positive DM status.\textsuperscript{66,67} In that case, it would affect the non-DM group, as these may potentially include DM patients, which thus could result in an underestimation of the effect size. Future research in relation to metabolic status should therefore preferably utilize only those participants who have been clinically diagnosed as DM or non-DM. The majority of the included studies (8 of 10) performed a clinical assessment for DM. Two included studies employed a questionnaire or self-report for DM status. The value of this self-report of disease in relation to medical records has been demonstrated to have high (≥90%) specificity but low sensitivity (66%) for DM.\textsuperscript{68}

**Evaluable number of teeth**
The number of evaluable teeth was assessed by professionally performed oral examinations to obtain optimally reliable values. Two studies that report the number of teeth by utilizing a questionnaire were therefore, in the second phase, excluded.\textsuperscript{69,70} However, both indicate numerically more missing teeth in the DM group as compared to healthy individuals.

Two of the included studies employ data based on 32 evaluable teeth and therefore include wisdom teeth (IX\textsuperscript{45} and VI\textsuperscript{49}), while the other eight evaluate 28 teeth. A subgroup analysis was performed with regard to the number of evaluated teeth. There was a numerical difference in RR of tooth loss between those studies evaluating 28 and 32 teeth (1.64 and 1.51, respectively), although the 95% CIs overlap ([95%CI 1.29;2.08] and [95%CI 1.45;1.58], respectively; see Figure 2 and Table 5a). Therefore, the difference of 0.13 between the RRs does not appear to be significant. Because of this lack of statistical difference for the other sub-analyses, the data from studies with either 28 or 32 evaluable teeth were not separated (see Table 5b as well as online Appendices S3-1 and S3-5). In the cases in which wisdom teeth are included in the evaluation, prophylactic removal should be considered as a reason for extraction. This aspect was not analyzed in the selected studies that evaluate 32 teeth. The numerically lower but non-significant difference in the analyses of 32 and 28 teeth could be influenced by this. The RR in the sub-analysis with 32 teeth was lower than those studies that evaluate 28 teeth. The lower association with DM could be, in part, the result of prophylactic removal.

**Geographical region**
From the included cross-sectional studies, the prevalence of DM is 16.8%. The World Health Organization (WHO) published in 2016\textsuperscript{71} the global DM prevalence as 9.2% for adults ≥18 years. This indicates that the data derived from the included studies are skewed toward DM, which in effect may provide an overestimation of the risk of tooth loss. A recent SR reports the prevalence of DM among subjects with periodontitis by continent. It indicates that the highest prevalence of DM was observed in studies from Asian countries (17.2%) and the lowest for those from Europe (4.3%).\textsuperscript{23} In the present review,
sub-analysis of the risk of tooth loss due to DM by world continent also demonstrates numerical differences. Asia (RR: 2.30) had the highest risk, followed by South America (RR: 2.27). The 95% CI of the RR of these two continents did not overlap with those of North America (RR: 1.22) or Europe (RR: 1.39), as both have a lower risk. Apart from comparable differences in the prevalence of DM, the differences in RR per region cannot readily be explained. What could contribute to the findings is that Asians are particularly susceptible to periodontitis and that DM is found to be more prevalent compared to other ethnic groups. The presumed relationship between DM and severity of periodontitis may then be seen as a possible explanation for the relatively high RR. However, no such explanation is available for the higher RR of tooth loss in South America. Study II evaluates a specific ethnic group (Hispanics or Latinos) and reports an RR that is lower than the overall RR of the present SR (1.13), which seems to be in line with Arora et al., who compared several ethnic groups in terms of oral health, lifestyle and usage of dental services in the United Kingdom. Individuals belonging to the non-White groups were less likely to report dental extractions and to have fewer than 20 teeth. This may reflect genuinely better oral health. The latter appears to explain the majority of the reduced risk found in Study II. However, a study from the USA suggests that Black individuals are more likely to choose dental extractions. This is mainly explained by preference, treatment acceptability and ability to afford treatment. A recent SR reports no difference for mean annual tooth loss when comparing geographic groups of North America, Europa, Japan and Oceania versus South America and Asia. Altogether, the above suggests that racial disparities could influence the observed tooth loss, although no clear explanation can be provided for the range in results as observed in the sub-analysis by geographical region.

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

Risk of bias
Assessment of risk of bias is a key step in conducting SRs and informs many other steps and decisions within the review. It also plays an important role in the final assessment of the strength of the evidence. Sub-analysis based on the overall estimated risk of bias of the selected studies indicates that for low risk of bias, a smaller RR (1.22 and 95% CI [1.20; 1.24]) was found than for those with a serious risk (RR = 1.48 at a 95% CI [1.45; 1.52]). The confidence interval for both low and serious risk of bias was small, which suggests that the estimate is not flawed by imprecision. If the review was restricted to only high methodological quality and low risk of bias studies, then the synthesis of the data concerning the number of teeth in DM patients as compared to non-DM individuals would indicate that the RR for tooth loss is rather small.
Limitations

- The language restriction to English resulted in three potential studies that had to be excluded. Two were in Spanish\textsuperscript{82,83}, and one was in Hungarian.\textsuperscript{84} Based on the information provided in the English abstract, it appears that in these three studies, tooth loss was greater among DM patients as compared to non-DM individuals. These results corroborate the present findings.
- Caries and periodontitis are the predominant reasons for tooth loss. None of the included studies provided details that could help discern what the indications for extraction had been.
- Factors such as differentiation between DM types I and II, type of assessment (self-report or professional), gender and age may have influenced the heterogeneity. This could not be further analyzed due to a lack of complete descriptions of the population included in the original studies.
- To summarize data from different geographical regions, it was decided to perform subgroup analysis on world continents. The reader should be aware that the reported studies may not capture the true RR of a specific world continent. Some studies have sampled only from small geographic regions, which may not represent the population of the continent.\textsuperscript{23}

Directions for further research

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

There is moderate certainty evidence for a small but significant higher risk of tooth loss in DM patients as compared to those without DM. Subgroup analysis showed that this was also higher if only DM type II was considered. If the data were separated by the world continent where the study was performed, analysis showed that the magnitude of the risk was particularly higher in Asia and South America.

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References

1. Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NH. Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. Health Qual Life Outcomes. 2010;8:126.
2. Ramseier CA, Anerud A, Dulac M, Lulic M, Cullinan, Seymour et al. Natural history of periodontitis: disease progression and tooth loss over 40 years. Journal of clinical periodontology. 2017;44(12):1182-91.
3. Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis et al. Periodontitis and diabetes: a two-way relationship. Diabetologia. 2012;55(1):21-31.
4. Löe H. Periodontal disease: the sixth complication of diabetes mellitus. Diabetes Care. 1993;16(1):329-34.
5. Selwitz RH, Ismail AI, Pitts NB. Dental caries. The Lancet. 2007;369(9555): 51-59.
6. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. The Journal of the American Dental Association. 2008;139:19S-24S.
7. International Diabetes Federation. IDF Diabetes Atlas, 6th edn. (International Diabetes Federation, 2013). Available from: http://www.idf.org/diabetesatlas.
8. Linden GJ, Herzberg MC, working group 4 of the joint EFP/AAP workshop Periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AA. Clinical Periodontology. 2013;S20-S23.
9. Mealey BL, Ocampo GL. Diabetes and periodontal disease. Perio. 2000. 2007; 44:127-153.
10. Chavarry NG, Vettore MV, Sansone C, Sheihaim A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. Oral health & preventive dentistry. 2009;7(2):107-27.
11. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with non-diabetics: a meta-analysis. Journal of Diabetes Complications. 2006;20(1): 59-68.
12. Jawed M, Shahid SM, Qader SA, Azhar A. Dental caries in diabetes mellitus: role of salivary flow rate and minerals. J Diabetes Complications. 2011;25(3):183-6.
13. Mascarenhas P, Fatela B, Barahona I. Effect of diabetes mellitus type 2 on salivary glucose- a systematic review and meta-analysis of observational studies. PLoS One. 2014;9(7):e101706.
14. American Diabetes Association. Standards of Medical Care in Diabetes-2019. Abridged for primary Care Providers. Clin Diabetes. 2019;37(1):11-34.
15. Page RC, Eke Pl. Case definitions for use in population based surveillance of periodontitis. J Periodontol. 2007;78(75):1387-99.
16. Helal O, Göstemeyer G, Krois J, El Sayed KF, Graetz C, Schwendicke F. Predictors for tooth loss in periodontitis patients: Systematic review and meta-analyses. Journal of clinical periodontology. 2019;46:699-712.
17. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. The Cochrane Collaboration. 2011. Available from: http://handbook-5-1.cochrane.org
18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of
observational studies in epidemiology: a proposal for reporting. Jama, Network. 2000; 283(15):2008-12.

19. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environment international. 2018;121:1027.

20. Morgan RL, Thayer KA, Santesso N, Holloway AC, Blain R, Eftim SE et al. A risk of bias instrument for non-randomized studies of exposures: a users’ guide to its application in the context of GRADE. Environment international. 2019;122:168-18.

21. Bero L, Chartres N, Diong J, Fabbri A, Ghersi D, Lam J et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. Systematic reviews. 2018;7(1):242.

22. Sterne JAC, Higgins JPT, Elbers RG, Reeves BC. The development group for ROBINS- I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance, updated 12 October 2016. Available from http://www.riskofbias.info [Accessed, 20 September, 2019]

23. Ziukaite L, Slot DE, Van der Weijden FA. Prevalence of diabetes mellitus in people clinically diagnosed with periodontitis: A systematic review and meta-analysis of epidemiologic studies. Journal of Clinical Periodontology. 2018;45(6):650-62.

24. RevMan: Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

25. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. J Chinese Integr Med. 2009;7(9):889–96.

26. Sambunjak D, Nickerson JW, Poklepovic T, Johnson TM, Imai P, et al. Flossing for the management of periodontal diseases and dental caries in adults. Cochrane Database of Systematic Reviews. 2011;(12): 26.

27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. Br Med J. 1997;315:629–34.

28. Ryan R. Heterogeneity and subgroup analyses in Cochrane Consumers and Communication Review Group reviews: planning the analysis at protocol stage. [Internet]. Cochrane Consum Commun Rev Group. 2016. Available from: http://cccrg.cochrane.org.

29. Van Swaaij BW, Van der Weijden GA., Bakker EW, Graziani F, Slot DE. Does chlorhexidine mouthwash, with an anti-discoloration system, reduce tooth surface discoloration without losing its efficacy? A systematic review and meta-analysis. International journal of dental hygiene. 2020;18(1), 27-43.

30. Community C. GRADE pro GDT Software [Internet]. Cochrane Community. Available from: http://community.cochrane.org/tools/review-production-tools/gradepro-gdt

31. Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: Development and pilot validation. Syst
32. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol. 2013;66(2):151–7.

33. Wiener, RC, Shen C, Findley PA, Sambaoorthi U Tan X. The association between diabetes mellitus, sugar-sweetened beverages, and tooth loss in adults: Evidence from 18 states. The Journal of the American Dental Association. 2017;148(7): 500-9.

34. Kapp JM, Boren SA, Yun S, LeMaster J. Peer Reviewed: Diabetes and Tooth Loss in a National Sample of Dentate Adults Reporting Annual Dental Visits. Preventing chronic disease. 2007;4(3).

35. Jung SH, Ryu JI, Jung DB. Association of total tooth loss with socio-behavioural health indicators in Korean elderly. Journal of oral rehabilitation. 2011;38(7): 517-24.

36. Oliver RC, Tervonen T. Periodontitis and tooth loss: comparing diabetics with the general population. The Journal of the American Dental Association. 1993;124(12): 71-76.

37. Yoo JJ, Kim DW, Kim MY, Kim YT, Yoon JH. The effect of diabetes on tooth loss caused by periodontal disease: A nationwide population-based cohort study in South Korea. Journal of Periodontology. 2019;90(6): 576-83.

38. Mayard-Pons ML, Rilliard F, Libersa JC, Musset AM, Farge P. Database analysis of a French type 2 diabetic population shows a specific age pattern of tooth extractions and correlates health care utilization. Journal of Diabetes and its Complications. 2015; 29(8), 993-97.

39. Jimenez M, Hu FB, Marino M, Li Y, Joshipura KJ. Type 2 diabetes mellitus and 20-year incidence of periodontitis and tooth loss. Diabetes research and clinical practice. 2011; 98(3): 494-500.

40. Costa FO, Miranda Cota LO, Pereira Lages EJ, Soares Dutra Oliveira AM, Dutra Oliveira PA, Cyrino RM, et al. Progression of periodontitis and tooth loss associated with glycemic control in individuals undergoing periodontal maintenance therapy: a 5-year follow-up study. Journal of periodontology. 2013;84(5):595-605. (Included paper ID #III)

41. Costa FO, Miranda Cota LO, Pereira Lages EJ, Vilela Câmara GC, Cortelli SC, Cortelli JR, et al. Oral impact on daily performance, personality traits, and compliance in periodontal maintenance therapy. Journal of periodontology. 2011;82(8):1146-54. (Included paper ID #III)

42. Shin HS. The number of teeth is inversely associated with metabolic syndrome: a Korean nationwide population-based study. Journal of periodontology. 2017;88(9):830-38. (Included paper ID #I)

43. Greenblatt AP, Salazar CR, Northridge ME, Kaplan RC, Taylor GW, Finlayson TL, et al. Association of diabetes with tooth loss in Hispanic/Latino adults: findings from the Hispanic Community Health Study/Study of Latinos. BMJ Open Diabetes Research and Care. 2016;4(1). (Included paper ID #II)

44. Kaur G, Holtfreter B, Rathmann WG, Schwahn C, Wallaschofski H, Schipf S, et al. Association between type 1 and type 2 diabetes with periodontal disease and tooth loss. Journal of clinical periodontology. 2009;36(9):765-74. (Included paper ID #VII)
45. Bačić M, Ciglar I, Granić M, Plančak D, Šutalo J. Dental status in a group of adult diabetic patients. Community dentistry and oral epidemiology. 1989;17(6):313-16. (Included paper ID #IX)
46. Falk H, Hugoson A, Thorstensson H. Number of teeth, prevalence of caries and periapical lesions in insulin-dependent diabetics. European Journal of Oral Sciences. 1989;97(3):198-206. (Included paper ID #X).
47. Patel MH, Kumarc JV, Moss ME. Diabetes and tooth loss: an analysis of data from the National Health and Nutrition Examination Survey, 2003–2004. The journal of the american dental association. 2013;144(5):478-85. (Included paper ID #IV)
48. Patiño Marin N, Loyola RJ, Medina SC, Pontigo, LA, Reyes MJ, Ortega RJ, et al. Caries, periodontal disease and tooth loss in patients with diabetes mellitus types 1 and 2. Acta Odontol Latinoam. 2007;21(2):127-33. (Included paper ID #VIII)
49. Sensorn W, Chatrchaiwiwatana S, Bumrerraj S. Relationship between diabetes mellitus and tooth loss in adults residing in Ubonratchathani province, Thailand. J Med Assoc Thai. 2012;95(12):1593-605. (Included paper ID #VI)
50. Botero JE, Yepes, FL, Roldán N, Castrillón, CA, Hincapie JP, Ochoa SP, et al. Tooth and periodontal clinical attachment loss are associated with hyperglycemia in patients with diabetes. Journal of periodontology. 2012;83(10):1245-50. (Included paper ID #V)
51. Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. Communications in Statistics-Theory and Methods. 2017;46(14):6774-81.
52. Chapple IL, Genco R, Working group 2 of the joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. Journal of Periodontology. 2013;84:S106-S112.
53. Chapple IL, Bouchard P, Cagetti MG, Campus G, Carra MC, Cocco F, et al. Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. Journal of clinical periodontology. 2017;44:S39-S51.
54. Marotta PS, Fontes TV, Armada L, Lima KC, Rocsas IN, Siqueira JF. Type 2 Diabetes Mellitus and the Prevalence of Apical Periodontitis and Endodontic Treatment in an Adult Brazilian Population. Journal of Endodontics. 2012;38(3).
55. Hopcraft MS, Morgan MV, Satur JG, Clive Wright FA. Edentulism and dental caries in Victorian nursing homes. The Gerodontology Society and John Wiley & Sons A/S Gerodontology. 2012;29:512-19.
56. Lopez-Lopez J, Jane-Salas E, Estrugo-Devesa A, Velasco-Ortega E, Martin-Gonzalez J, Segura-Egea JJ. Periapical and Endodontic Status of Type II Diabetic Patients in Catalonia, Spain: A Cross-sectional Study. Journal of Endodontics. 2011;37(5).
57. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. Bmj. 2010;340.
58. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PloS one. 2008;3(8):e3081.

59. Lagervall M, Jansson L. Relationship between tooth loss/probing depth and systemic disorders in periodontal patients. Swedish dental journal. 2007;31;(1):1-9.

60. Aoyama N, Suzuki JI, Kobayashi N, Hanatani T, Ashigaki N, Yoshida A, et al. Japanese cardiovascular disease patients with diabetes mellitus suffer increased tooth loss in comparison to those without diabetes mellitus-a cross-sectional study. Internal Medicine. 2018;57;(6):777-82.

61. International Diabetes Federation. IDF diabetes Atlas Ninth [Internet]. Dunia IDF. 2019. Available from: https://www.diabetesatlas.org/en/.

62. Sterne JA, Egger M, Smith GD. Investigating and dealing with publication and other biases in meta-analysis. Bmj. 2001; 323(7304):101-5.

63. Lundh A, Sismondo S, Busuio O, Bero L. Industry Sponsorship and Research Outcome. JAMA Intern Med [Internet]. 2013;173(7):580. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2013.4190.

64. Tuso P. Prediabetes and lifestyle modification: time to prevent a preventable disease. The Permanente Journal. 2014;18(3):88.

65. International Diabetes Federation. [Internet]. What is diabetes. Available from: https://idf.org/aboutdiabetes/what-is-diabetes.html.

66. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. [Internet]. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011. Available from: www.cdc.gov/diabetes/pubs/pdf/ndfs_2011_pdf.

67. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of periodontitis in adults in the United States: 2009 and 2010. Journal of Dental Research. 2012;91:914-920.

68. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. Journal of clinical epidemiology. 2004;57(10):1096-1103.

69. Hastings JF, Vasquez E. Diabetes and Tooth Loss among Working-Age African Americans: A National Perspective. Social work in public health. 2017;32(7):443-51.

70. Similä T, Auvinen J, Puukka K, Keinänen-Kiukaanniemi S, Virtanen Jl. Impaired glucose metabolism is associated with tooth loss in middle-aged adults: The Northern Finland Birth Cohort Study 1966. Diabetes research and clinical practice. 2018;142:110-19.

71. World Health Organization. Diabetes Global Prevalence [Internet]. 2016. Available from: http://www.who.int/mediacentre/factsheets/fs312/en/.

72. Corbet EF, Leung WK. Epidemiology of periodontitis in the Asia and Oceanic regions. Periodontol 2000;56:25–64.
73. Huxley R, James WP, Barzi F, Patel JV, Lear SA, Suriyawongpaisal P, et al. Obesity in Asia Collaboration. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obes Rev 2008;(1):53–61.
74. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA. 2009;301(20):2129-40.
75. Arora G, Mackay DF, Conway DI, Pell JP. Ethnic differences in oral health and use of dental services: cross-sectional study using the 2009 Adult Dental Health Survey. BMC Oral Health. 2017;17(1):1.
76. Tilashalski KR, Gilbert GH, Boykin MJ, Litaker MS. Racial differences in treatment preferences: oral health as an example. J Eval Clin Pract. 2007;13(1):102–8.
77. Needleman I, Garcia R, Gkranias N, Kirkwood KL, Kocher T, Iorio AD, et al. Mean annual attachment, bone level, and tooth loss: A systematic review. Journal of clinical periodontology. 2018;45:S112-S129.
78. Diabetes, U. K. Diabetes in the UK 2010: key statistics on diabetes. London: Diabetes UK. [Internet]. 2010. Available from: https://www.diabetes.org.uk/resources-s3/2017-11/diabetes_in_the_uk_2010.pdf.
79. Liu Y, Yu Y, Nickel JC, Iwasaki LR, Duan P, Simmer-Beck M, et al. Gender differences in the association of periodontitis and type 2 diabetes. International dental journal. 2018; 68(6):433-40.
80. Baskaradoss JK. Relationship between oral health literacy and oral health status. BMC Oral Health. 2018;18(1):172.
81. Viswanathan M, Patnode CD, Berkman ND, Bass EB, Chang S, Hartling L et al. Assessing the risk of bias in systematic reviews of health care interventions. In Methods guide for effectiveness and comparative effectiveness reviews [Internet]. 2017. Agency for Healthcare Research and Quality (US).
82. Sampedro CA, Segura JE, Lapetra JP, Llamas RC. Diabetes as a risk factor for tooth loss in the geriatric population. Atencion primaria. 1996;18(4):182-5.
83. López-López J, Jané-Salas E, Estrugo-Devesa A, Velasco-Ortega E, Martín-González J, Segura-Egea JJ. Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: a cross-sectional study. Journal of endodontics. 2011;37(5):598-601.
84. Albrecht M, Banoczy J, Dinya E, Tamas Jr. G. Caries status in diabetic patients. Fogorvosi szemle. 1991;84(9):267.
Table 1
Search terms used for PubMed-MEDLINE. The search strategy was customized according to the database being searched.

The following strategy was used in the search:

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

| [{[<exposure>] AND [<outcome>]}] |
|---------------------------------|
| [{[<exposure>] (“diabetes mellitus” [Mesh] OR diabetes OR (diabetes mellitus)[textwords])}] AND [<outcome>] (tooth loss) OR (toothloss) OR (teeth loss) OR (teethloss) OR (toothless) OR (toothless) OR (missing teeth) OR (missing tooth) OR (loss of teeth) OR (loss of tooth) OR (number of teeth) OR (number of tooth))) OR tooth loss [MeSH Terms]) OR number of teeth [MeSH Terms]) |

The asterisk (*) was used as a truncation symbol.
Table 2
Overview of the studies processed for data extraction

| Selection ID | N | Type of population | Gender (N males, N females) | Mean age (SD) | Range in years | Type of DM and type of assessment | # teeth in patients with DM | Total N of teeth used for calculations | # teeth in people non-DM | Total N of teeth used for calculations |
|--------------|---|-------------------|-----------------------------|---------------|----------------|-----------------------------------|-----------------------------|---------------------------------------|-------------------------------|--------------------------------------|
| Shin et al. 2017 | Total: 12131 ♦ | | | | | | | | | |
| Cross-sectional | DM: 1295 ♦ | | | | | | | | | |
| Korea | Non-DM: 10836 ♦ | | | | | | | | | |
| Rob: Moderate | | Selected from KNHANES, a study periodically conducted by the Korea Centre for Disease Control and Prevention (KCDC), in 2012-2014. | | | | | | | | | |
| | Total: 5342 ♦ | | | | | | | | | |
| | ♀ 6789 ♦ | | | | | | | | | |
| | Mean age: ? | | | | | | | | | |
| | DM ♀: ? | | | | | | | | | |
| | ♀: ? | | | | | | | | | |
| | Mean age: ? | | | | | | | | | |
| | Non-DM ♀: ? | | | | | | | | | |
| | ♀: ? | | | | | | | | | |
| | Mean age: ? | | | | | | | | | |
| | DM type II | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| | DM: ? | | | | | | | | | |
| | Type of assessment: Prof-D | | | | | | | | | |
| Study | Total | DM | Poorly control | Well control | Missing | Total teeth | Patient level |
|-------|-------|----|----------------|-------------|---------|-------------|--------------|
| Greenblatt et al. 2016 | Total: 9271 | DM: 2792 | Uncontrolled: 1324 | Controlled: 1468 | | | |
|  | Total: 6089 | DM: | | | | | |
| Prospective cohort | Non-DM: 6479 | Non-DM: | | | | | |
| United States | | | | | | | |
| RoB: Low | | | | | | | |
| Costa et al. 2013/2011 | Total: 92 | DM: 46 | Poorly control: 23 | Well control: 23 | | | |
| Case-controlled | Total: 40 | DM: | | | | | |
|  | Total: 52 | Non-DM: | | | | | |
|  | | | | | | | |
| Country          | Population Description                          | DM Type | Non-DM | Mean Age | Poor Control | Well Control | Mean Age | Poor Control | Well Control | Mean Age |
|------------------|-------------------------------------------------|---------|--------|----------|--------------|--------------|----------|--------------|--------------|----------|
| Brazil           | Cohort undergoing PMT                           | DM      | Non-DM | ?        |              |              |          |              |              |          |
|                  |                                                 | ♂ 20    | ♂ 20   |          | ♂ 10        | ♂ 10         |          | ♂ 10         | ♂ 10         |          |
|                  |                                                 | ♀ 26    | ♀ 26   |          | ♀ 13        | ♀ 13         |          | ♀ 13         | ♀ 13         |          |
| IV Patel et al. | 2013 Cross-sectional United States              | DM type I/II |      |          |              |              |          |              |              |          |
|                  | General population from the NHANES sample      | Total: 2055 |     |          | Total: 992 | Total: 1063 |          | Total: 1063 | Total: 1063 |          |
|                  |                                                 | ♂ 992  | ♂ 1063 |          | ♂ ?         | ♂ ?          |          | ♂ ?          | ♂ ?          |          |
|                  |                                                 | ♀ 1063 | ♀ ?    |          | ♀ ?         | ♀ ?          |          | ♀ ?          | ♀ ?          |          |

*Based on 28 teeth*
| Study            | Total:       | With DM:   | Non-DM:    | Mean age (♂): | Mean age (♀): | DM type I/II | Missing: | Total teeth: | Patient level: |
|------------------|--------------|------------|------------|---------------|---------------|--------------|----------|--------------|----------------|
| Botero et al.    | 124          | 65         | 59         | ?             | 57.4          | DM          | 481      | 1820         | 20.6 T+ 7.4 T- |
| Location         | Cross-sectional | Colombia  | Hospital Universitario | San Vicente de Paul (Medellin, Colombia) | Non-DM: 59 | | | | | |
| RoB: Moderate    | 67 (♂) 57 (♀) | 45 (♂) 20 (♀) | 22 (♂) 37 (♀) | Mean age: ? | Mean age: 44.1 | | | | | |
| Sensorn et al.   | 605          | 379        | 226        | 20-86         | | DM type I/II | 2414     | 12128        | 25.63 T+ | 28.93 T+ |
| Location         | Cross-sectional | Colombia  | School of Dentistry at the Universidad del Valle | | | | | | | |
Thailand
RoB: Serious
General population living in Nachaluay district, Ubonratchathani, Thailand.

DM
♂: 72 ♦
♀: 307 ♦
Mean age: 54.7 ♦
Non-DM
♂: 58 ♦
♀: 168 ♦
Mean age: 43.6 ♦

6.37 T- ♦
Based on 32 teeth ♦

3.07 T- ♦
Based on 32 teeth ♦

VII: Kaur et al. 2009
Cross-sectional
Germany
RoB: Low
General population from the SHIP Trend study (population-based survey in North-Eastern Germany)
T1DM: Centre of Cardiology and Diabetes, Karlsburg

Total: 4288 ♦
DM: 327 ◊
DM I: 145 ♦
DM II: 182 ♦
Non-DM: 3961 ◊

Total
♂: 2055 ◊
♀: 2233 ◊
Mean age: ?

DM
♂: 180 ◊
♀: 147 ◊
Mean age: 52.5 ◊

Type of assessment: T1DM Prof-D
SHIP/T2DM: Self-R

Type of assessment: Self-R (T1DM) and/or Prof-D (T2DM)

Missing: 3414 ◊
Total teeth: 9156 ◊
Patient level:
18 T+ ◊
10 T- ◊

Based on 28 teeth ◊

Total: 110908 ◊
Missing: 282184 ◊
Total teeth ever: 74116 ◊
Patient level:
Non-DM (compared DMI&II)
19.9 T+ ◊
8.1 T- ◊

Based on 28 teeth ◊

Non-DM (compared DM II)
Missing: 14454 ◊
Total teeth: 36792 ◊
Patient level:
22.8 present teeth ◊
5.2 missing teeth ◊
Non-DM (compared DM I)
Missing: 13764 ◊
Total teeth: 4060 ◊
Patient level:
21.9 present teeth ◊
6.1 missing teeth ◊

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| VIII: Patiño-Marin et al. 2008 | Total: 70 ♂ 35 ♀ 46.8 Mean age: Mean age: | Patient level: 14.1 T+ 13.9 T- | Mean age: ? Mean age: 45 Mean age: 42 Mean age: 42 |
|--------------------------------|---------------------------------------------|--------------------------------|---------------------------------------------|
| Cross-sectional               | DM: 35 ♂ 46 ♀ 46 Mean age: ?               | Patient level: 17.0 T+ 11.0 T- | Non-DM: 19 ♂ 25 ♀ 45 Mean age: 42 Mean age: 45 |
| Mexico                        | Non-DM: 35 ♂ 46 ♀ 46 Mean age: ?           | Missing: 123 ♂ 46 ♀ 46 Mean age: | DM: 14 ♂ 21 ♀ 46 Mean age: 46 Mean age: 46 Mean age: 46 |
| RoB: Moderate                 | Mean age: ? Mean age: 45 Mean age: 42 Mean age: | Missing: 200 ♂ 46 ♀ 46 Mean age: | Non-DM: 19 ♂ 25 ♀ 46 Mean age: 46 Mean age: 46 Mean age: 46 |
|                               | DM type II Missing: 2731 ♂ 46 ♀ 46 Mean age: | Total teeth: 980 ♂ 46 ♀ 46 Mean age: | DM type II Missing: 1833 ♂ 46 ♀ 46 Mean age: |
|                               | Type of assessment: Prof-D Patient level: 22.3 T+ 5.7 T- Based on 28 teeth Based on 28 teeth | Patient level: 24.5 T+ 3.5 T- Based on 28 teeth Based on 28 teeth | Type of assessment: Prof-D Patient level: 19.7 T+ 12.3 T- Based on 32 teeth Based on 32 teeth |
| IX: Bacic et al. 1989         | Total: 411 ♂ 245 ♀ 49.6 Mean age: Patient level: 19.7 T+ 12.3 T- Based on 32 teeth Based on 32 teeth | Missing: 2731 ♂ 46 ♀ 46 Mean age: | DM: 130 ♂ 92 ♀ 49.6 Mean age: 49.6 Mean age: 49.6 Mean age: 49.6 |
| Cross-sectional               | DM: 222 ♂ 166 ♀ 49.6 Mean age: Patient level: 19.7 T+ 12.3 T- Based on 32 teeth Based on 32 teeth | Total teeth: 7104 ♂ 46 ♀ 46 Mean age: | DM: 130 ♂ 92 ♀ 49.6 Mean age: 49.6 Mean age: 49.6 Mean age: 49.6 |
| Croatia                       | Insulin dependent (IDDM): 109 ♂ 92 ♀ 49.6 Mean age: Patient level: 19.7 T+ 12.3 T- Based on 32 teeth Based on 32 teeth | Total teeth: 6048 ♂ 46 ♀ 46 Mean age: | Insulin dependent (IDDM): 109 ♂ 92 ♀ 49.6 Mean age: 49.6 Mean age: 49.6 Mean age: 49.6 |
| RoB: Serious                  | Non-insulin dependent (NIDDM) 113 ♂ 64 ♂ 49.6 Mean age: Patient level: 19.7 T+ 12.3 T- Based on 32 teeth Based on 32 teeth | Missing: 1833 ♂ 46 ♀ 46 Mean age: | Non-insulin dependent (NIDDM) 113 ♂ 64 ♂ 49.6 Mean age: 49.6 Mean age: 49.6 Mean age: 49.6 |
Metabolic Diseases in Zagreb referred from all parts of Croatia.

Non-DM: 189 ♦

Non-DM patients: general population of Croatia during a survey on the prevalence of periodontal disease and caries in Croatia.

Non-DM:
♂: 115 ♦
♀: 74 ♦
Mean age: 43.9 ♦
| Study | Total | DM | Non-DM | General population |
|------|-------|----|--------|---------------------|
| Falk et al. 1989 | 231 | 154 | 77 | selected from the county council's register of persons residing in the borough of Jonkoping. |
| Cross-sectional | 112 ♀ | 119 ♂ | 77 ♀ | 43 ♂ | selected from the Department of medicine at the central Hospital in Jönköping, Sweden. |
| Sweden | DM: 82 (28.9 years) | Short duration: 72 (5.2 years) | | |
| RoB: Moderate | | | | |
| | Long duration ♂: 40 | ♂: 34 | ♂: 34 | ♀: 34 | |
| | Short duration ♂: 38 | ♀: 42 | ♀: 43 | |
| DM type I/II | ♂: 78 | ♂: 76 | ♂: 76 | |
| Type of assessment: | Mean age: ? | Mean age: ? | Mean age: ? (20-70) | |
| Missing | 1007 | Total teeth: 4312 | | |
| | Total teeth: 2156 | Patient level: | |
| | | 21.4 T+ | 6.6 T- |
| | | Based on 28 teeth | |
| | | Long duration | |
| | | Patient level: | |
| | | 22.3 T+ | 5.7 T- |
| | | Based on 28 teeth | |
| | | Long duration | |
| | | Patient level: | |
| | | 20.5 T+ | 7.5 T- |
| Abbreviation | Meaning |
|--------------|---------|
| PMT          | Periodontal maintenance therapy |
| PrDM         | Previous known diabetes mellitus |
| Prof D       | Professionally diagnosed |
| RoB          | Risk of bias |
| ScDM         | Screening detected diabetes mellitus |
| Self-R       | Self-reported |
| Type I/II    | No distinction is made between type of diabetes |
| Type I and/or II: | Distinction is made between diabetes type I and II |
| T1DM         | Type 1 diabetes |
| T2DM         | Type 2 diabetes |
| T+           | Present teeth |
| T-           | Missing teeth |
| ◊            | Calculated |
| ♦            | Given by the original author |
| ?            | Is not reported/unknown |
Table 3
Summary of the risk of bias assessment using Robins-E tool

| Study ID | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of exposures | Bias due to departures from intended exposures | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall Risk of bias | For detail see online appendix |
|----------|-------------------------|-----------------------------------------------|------------------------------------|-----------------------------------------------|-------------------------|-------------------------------|----------------------------------------|---------------------|-----------------------------|
| I        | Moderate                | Low                                           | Low                                | Moderate                                       | Low                     | Low                           | Low                                    | Moderate            | S2-2                        |
| II       | Low                     | Low                                           | Low                                | Low                                           | Low                     | Low                           | Low                                    | Low                 | S2-3                        |
| III      | Moderate                | Moderate                                       | Low                                | Low                                           | Low                     | Low                           | Low                                    | Moderate            | S2-4                        |
| IV       | Low                     | Low                                           | Moderate                           | Serious                                        | Moderate                | Low                           | Low                                    | Serious             | S2-5                        |
| V        | Moderate                | Moderate                                       | Moderate                           | Moderate                                       | Low                     | Low                           | Low                                    | Moderate            | S2-6                        |
| VI       | Low                     | Serious                                        | Serious                            | Moderate                                       | Low                     | Low                           | Low                                    | Serious             | S2-7                        |
| VII      | Low                     | Low                                           | Low                                | Low                                           | Low                     | Low                           | Low                                    | Low                 | S2-8                        |
| VIII     | Moderate                | Moderate                                       | Low                                | Low                                           | No information          | Low                           | Low                                    | Moderate            | S2-9                        |
| IX       | Serious                 | Moderate                                       | Low                                | Moderate                                       | Low                     | Low                           | Moderate                              | Serious             | S2-10                       |
| X        | Moderate                | Low                                           | Moderate                           | Moderate                                       | Low                     | Low                           | Moderate                              | Moderate            | S2-11                       |
Table 4
A descriptive summary of statistical significance levels of the difference between DM patients compared to non-DM with regard to number of teeth.

| study          | exposure | Number of teeth significance | comparison |
|----------------|----------|------------------------------|------------|
| 1. Shin et al. 2017 | DM       | ?                            | non-DM     |
| 2. Greenblatt et al. 2016 | DM       | ?                            | non-DM     |
| 3. Costa et al. 2011/2013 | DM       | +                            | non-DM     |
| 4. Patel et al. 2013 | DM       | +                            | non-DM     |
| 5. Botero et al. 2012 | DM       | +                            | non-DM     |
| 6. Sensorn et al. 2012 | DM       | +                            | non-DM     |
| 7. Kaur et al. 2009 | DM       | ?                            | non-DM     |
| 8. Patiño-Marín et al. 2008 | DM       | +                            | non-DM     |
| 9. Bacic et al. 1989 | DM       | +                            | non-DM     |
| 10. Falk et al. 1989 | DM       | ?                            | non-DM     |
| Total          |          | 6/10 have significant less teeth |          |
|                |          | 0/10 no significant difference |          |
|                |          | 4/0 do not specified          |          |

? unclear/not specified
0 no difference
DM patients have significant less teeth than non-DM
Table 5a
Overview (sub) analysis overall and evaluable number of teeth (28/32).

|                        | Effect sizes | Heterogeneity | Funnel plot appendix | For details see |
|------------------------|--------------|---------------|----------------------|-----------------|
|                        | Included studies | RR | model | 95 CI% | p-value | I² value | P-value |                     |                 |
| Overall                | 12 studies    | 1.63 | random | [1.33-2.00] | <0.00001 | 100% | < 0.00001 | S4 | Table 5a |
| Number of teeth        |              |     |       |        |         |     |         |     |                     |
| 32 teeth               | Bacic et al. 1989  | 1.51 | fixed | [1.45-1.58] | <0.00001 | 99% | < 0.00001 | S4 | Table 5a |
|                        | Sensorn et al. 2012 |     |       |        |         |     |         |     |                     |
| 28 teeth               | Botero et al 2012 | 1.64 | random | [1.29-2.08] | <0.00001 | 100% | < 0.00001 | S4 | Table 5a |
|                        | Costa et al. 2011/2013 |     |       |        |         |     |         |     |                     |
|                        | Falk et al. 1989 |     |       |        |         |     |         |     |                     |
|                        | Greenblatt et al. 2016 |     |       |        |         |     |         |     |                     |
|                        | Kaur et al. 2009 |     |       |        |         |     |         |     |                     |
|                        | Patel et al. 2013 |     |       |        |         |     |         |     |                     |
|                        | Patiño-Marín et al. 2008 |     |       |        |         |     |         |     |                     |
|                        | Shin et al. 2017 |     |       |        |         |     |         |     |                     |
Table 5b
Overview sub-analysis: risk of bias, study design, world continent, DM type II, DM status

| Risk of bias | Included studies | RR    | model | 95C%       | p-value   | I² value | P value   | Funnel plot | For details see |
|--------------|------------------|-------|-------|------------|-----------|----------|-----------|-------------|-----------------|
| Low          | Greenblatt et al. 2016 | 1.22  | Fixed | [1.20-1.24] | < 0.00001 | 100%     | < 0.00001 | S4          | S3-1            |
|              | Kaur et al. 2009  |       |       |            |           |          |           |             |                 |
| Moderate      | Botero et al 2012 | 1.85  | Random| [1.27-2.71] | 0.001     | 98%      | < 0.00001 | S4          | S3-1            |
|              | Falk et al. 1989  |       |       |            |           |          |           |             |                 |
|              | Patiño-Marín et al. 2008 |       |       |            |           |          |           |             |                 |
|              | Costa et al. 2013/2011 |       |       |            |           |          |           |             |                 |
|              | Shin et al. 2017  |       |       |            |           |          |           |             |                 |
| Serious       | Patel et al. 2013 | 1.48  | Fixed | [1.45-1.52] | < 0.00001 | 98%      | < 0.00001 | S4          | S3-1            |
|              | Bagic et al. 1989 |       |       |            |           |          |           |             |                 |
|              | Sensorn et al. 2012 |       |       |            |           |          |           |             |                 |
| Study design  | Cross-sectional  | Botero et al 2012 | 1.77  | Random | [1.44-2.17] | < 0.00001 | 99%      | < 0.00001 | S4          | S3-2            |
|              | Falk et al. 1989  |       |       |            |           |          |           |             |                 |
|              | Kaur et al. 2009  |       |       |            |           |          |           |             |                 |
|              | Patel et al. 2013 |       |       |            |           |          |           |             |                 |
|              | Patiño-Marín et al. 2008 |       |       |            |           |          |           |             |                 |
|              | Shin et al. 2017  |       |       |            |           |          |           |             |                 |
|              | Bagic et al. 1989 |       |       |            |           |          |           |             |                 |
|              | Sensorn et al. 2012 |       |       |            |           |          |           |             |                 |

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| World continent | Study (year) | F-statistic | Fixed/Random | 95% CI | P-value | Type 1 Diabetes | Type 2 Diabetes |
|-----------------|--------------|-------------|--------------|--------|---------|----------------|----------------|
| Europe          | Kaur et al. 2009, Bacic et al. 1989, Falk et al. 1989 | 1.39 | fixed | [1.35-1.42] | <0.00001 | 94% | < 0.00001 |
| North- America  | Greenblatt et al. 2016, Patel et al. 2013, Patiño Marín et al. 2008 | 1.22 | fixed | [1.20-1.24] | <0.00001 | 99% | < 0.00001 |
| Asia            | Shin et al. 2017, Sensorn et al. 2012 | 2.30 | fixed | [2.25-2.36] | < 0.00001 | 88% | 0.004 |
| South- America  | Costa et al. 2013/2011, Botero et al. 2012 | 2.27 | fixed | [2.00-2.58] | <0.00001 | 99% | < 0.00001 |
| Solely diagnosed as DM type II | | | | | | | |
| Type II         | Shin et al. 2017, Costa et al. 2011/2013, Kaur et al. 2009, Patino-Marín et al. 2008 | 1.56 | random | [1.02-2.39] | 0.04 | 100% | <0.00001 |
| Diabetic status | | | | | | | |
| Well controlled vs non-DM | Greenblatt et al. 2016, Costa et al. 2011/2013 | 1.03 | fixed | [1.00-1.06] | 0.04 | 0% | 0.88 |
| Poor controlled vs non-DM | Greenblatt et al. 2016, Costa et al. 2011/2013 | 1.25 | fixed | [1.22-1.29] | <0.00001 | 23% | 0.25 |
| Poor vs well controlled DM | Greenblatt et al. 2016, Costa et al. 2011/2013 | 1.21 | fixed | [1.17-1.26] | <0.00001 | 0% | 0.41 |
Table 6
GRADE evidence profile for the number of teeth and risk ratio among DM as compared to non-DM.

| Determinants of Quality                        | Risk Ratio                                      |
|-----------------------------------------------|------------------------------------------------|
| Study design (Table 2)                        | Observational studies                           |
| #studies (figure 1)                           | # 10                                            |
| #comparisons                                  | # 10                                            |
| Risk of bias (Table 3, Appendix S2)           | Low to serious                                  |
| Consistency (Table 2)                         | Rather inconsistent                             |
| Directness                                    | Rather generalizable                            |
| Precision (Figure 2, Table 5 Online appendix S3) | Rather precise                                |
| Reporting bias                                | Likely                                          |
| Magnitude of the effect (Figure 2, Table 5 Online appendix S3) | Small                                          |
| Strength of the recommendation based on the quality and body of evidence | Moderate                                       |
| Direction of recommendation                   | With respect to tooth loss, there is moderate certainty for a small risk for DM over non-DM. |
Figure 2.1

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

| Study or Subgroup          | DM Events | DM Total | no DM Events | no DM Total | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|---------------------------|-----------|----------|--------------|-------------|--------|--------------------------------|--------------------------------|
| 2.1.1 28 teeth            |           |          |              |             |        |                                |                                |
| Botero et al. 2012        | 481       | 1820     | 112          | 1652        | 9.4%   | 3.90 [3.21, 4.74]              |                                |
| Costa et al. 2011/2013    | 225       | 1288     | 183          | 1288        | 9.6%   | 1.23 [1.03, 1.47]              |                                |
| Falk et al. 1986          | 1007      | 4312     | 416          | 2156        | 10.1%  | 1.21 [1.09, 1.34]              |                                |
| Greenblatt et al. 2016    | 10140     | 78176    | 20733        | 181412      | 10.3%  | 1.13 [1.11, 1.16]              |                                |
| Kaur et al. 2009          | 3414      | 9156     | 28218        | 110908      | 10.3%  | 1.47 [1.42, 1.51]              |                                |
| Patel et al. 2013         | 3763      | 10752    | 11196        | 46788       | 10.3%  | 1.46 [1.42, 1.51]              |                                |
| Patino-Márin et al. 2008  | 200       | 980      | 123          | 980         | 9.3%   | 1.63 [1.32, 2.00]              |                                |
| Shin et al. 2017          | 7356      | 36260    | 26331        | 303408      | 10.3%  | 2.34 [2.28, 2.39]              |                                |
| Subtotal (95% CI)         | 142744    | 648592   | 79.6%        |             |        | 1.54 [1.29, 2.08]              |                                |
| Total events              | 26586     | 87312    |              |             |        |                                |                                |
| Heterogeneity: Tau² = 0.12; Chi² = 2103.74, df = 7 (P < 0.00001); I² = 100% |
| Test for overall effect: Z = 4.04 (P < 0.0001) |

2.1.2 32 teeth

| Study or Subgroup          | DM Events | DM Total | no DM Events | no DM Total | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|---------------------------|-----------|----------|--------------|-------------|--------|--------------------------------|--------------------------------|
| Back et al. 1989          | 2731      | 7104     | 1833         | 6048        | 10.3%  | 1.27 [1.21, 1.33]              |                                |
| Sensorn et al. 2012       | 2414      | 12128    | 694          | 7232        | 10.2%  | 2.67 [1.92, 2.25]              |                                |
| Subtotal (95% CI)         | 19232     | 32532    | 20.4%        |             |        | 1.52 [0.99, 2.65]              |                                |
| Total events              | 5145      | 2527     |              |             |        |                                |                                |
| Heterogeneity: Tau² = 0.12; Chi² = 112.39, df = 1 (P < 0.00001); I² = 99% |
| Test for overall effect: Z = 1.92 (P = 0.05) |

| Total (95% CI)            | 161976    | 661872   | 100.0%       |             | 1.63 [1.33, 2.00]              |                                |
| Total events              | 31731     | 89839    |              |             | 1.11 [2.78]                    |                                |
| Heterogeneity: Tau² = 0.11; Chi² = 2212.78, df = 9 (P < 0.00001); I² = 100% |
| Test for overall effect: Z = 4.70 (P < 0.00001) |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0% |

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

| Study or Subgroup | DM Events | DM Total | no DM Events | no DM Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-----------|----------|--------------|-------------|--------|-------------------------------|-------------------------------|
| Botero et al. 2012 | 481       | 1820     | 112          | 1652        | 0.4%   | 3.90 [3.21, 4.74]             |                               |
| Costa et al. 2011/2013 | 225      | 1288     | 183          | 1288        | 0.6%   | 1.23 [1.03, 1.47]             |                               |
| Falk et al. 1988  | 1007      | 4312     | 416          | 2156        | 1.8%   | 1.21 [1.09, 1.34]             |                               |
| Greenblatt et al. 2016 | 10140    | 78176    | 20733        | 181412      | 41.0%  | 1.13 [1.11, 1.16]             |                               |
| Kaur et al. 2009   | 3414      | 9156     | 28218        | 110008      | 14.1%  | 1.47 [1.42, 1.51]             |                               |
| Patel et al. 2013  | 3763      | 10752    | 11196        | 46788       | 13.8%  | 1.46 [1.42, 1.51]             |                               |
| Patino-Marin et al. 2008 | 200      | 980      | 123          | 980         | 0.4%   | 1.63 [1.32, 2.00]             |                               |
| Shin et al. 2017   | 7356      | 36260    | 26331        | 303408      | 18.5%  | 2.34 [2.28, 2.39]             |                               |
| Subtotal (95% CI) |           | 142744   | 648592       |             | 90.6%  | 1.50 [1.48, 1.52]             |                               |

Total events 26586, 87312
Heterogeneity: $\chi^2 = 2103.74$, df = 7 ($p < 0.00001$); $\hat{I}^2 = 100$
Test for overall effect: $Z = 62.63$ ($p < 0.00001$)

2.1.2 32 teeth

| Study or Subgroup | DM Events | DM Total | no DM Events | no DM Total | Weight | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-----------|----------|--------------|-------------|--------|-------------------------------|-------------------------------|
| Basic et al. 1989 | 2731      | 7104     | 1833         | 6048        | 6.5%   | 1.27 [1.21, 1.33]             |                               |
| Sensorn et al. 2012 | 2414    | 12128    | 694          | 7232        | 2.9%   | 2.07 [1.92, 2.25]             |                               |
| Subtotal (95% CI) |           | 19232    | 13280        |             | 9.4%   | 1.51 [1.43, 1.58]             |                               |

Total events 5145, 2527
Heterogeneity: $\chi^2 = 112.39$, df = 1 ($p < 0.00001$); $\hat{I}^2 = 98$
Test for overall effect: $Z = 19.49$ ($p < 0.00001$)

Total (95% CI) 161976, 661872 100.0% 1.50 [1.48, 1.52]
Total events 31731, 89839
Heterogeneity: $\chi^2 = 2212.78$, df = 9 ($p < 0.000001$); $\hat{I}^2 = 100$
Test for overall effect: $Z = 65.57$ ($p < 0.00001$)
Test for subgroup differences: $\chi^2 = 0.25$, df = 1 ($p = 0.62$), $\hat{I}^2 = 0$

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