REVIEW ARTICLE

Tooth Loss is a Risk Factor for Cardiovascular Disease Mortality: A Systematic Review with Meta-analyses

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SIGNIFICANCE

The findings of the current review support the concept that being edentulous or having less than 10 teeth may be associated with CVD mortality.

ABSTRACT

Introduction: The current evidence linking tooth loss and cardiovascular disease mortality is inconclusive. Thus, the aim of this systematic review was to explore the association between tooth loss and cardiovascular disease (CVD) mortality. **Methods:** A comprehensive literature search of databases and gray literature included: Web of Science, Scopus, PubMed, Cochrane Central Register of Controlled Trials, Google Scholar, various digital repositories. The included studies reported on CVD mortality and tooth loss. The Newcastle-Ottawa scale was used to assess the quality of included studies. Random-effects meta-analysis method, sub-group analysis (based on the tooth loss categories (edentulous and fewer than 10 teeth present), meta-regression (based on the number. of confounders), publication bias, and sensitivity analysis were performed. **Results:** Twelve articles met the eligibility criteria with an overall "Good" quality. A significant association between tooth loss (edentulous or less than 10 teeth present) and CVD mortality was found in the primary meta-analysis, which compiled data from 12 studies. The estimated hazard ratio was 1.66 (95% CI: 1.32–2.09), and there was high heterogeneity (I^2 = 82.42). Subgroup analysis revealed that the edentulous sub-group showed a higher risk with no significant heterogeneity, while the subgroup with fewer than 10 teeth showed a higher risk with substantial heterogeneity. Meta-regression analysis did not reveal any significant impact (P = .626) on whether variations in the number of con-founders across studies would substantially affect the overall findings. No publication bias was detected and the sensitivity analysis based on the critical confounders also confirmed that tooth loss as a risk factor for CVD mortality (hazard ratio = 1.52, 95% CI: 1.28–1.80), (I^2 51.82%). **Conclusion:** The present systematic review reported that being edentulous or having lesser than 10 teeth is a predictive indicator of CVD mortality. *(J Endod 2024;50:1370–1380.)*

KEY WORDS

Cardiovascular disease; endodontics; missing tooth; mortality; systematic review; tooth loss

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Cardiovascular disease (CVD) remains as one of the leading causes of death and it has caused social and economic disturbances around the world in the last few decades[1,2]. In 2019, 17.9 million individuals died due to CVDs worldwide, accounting for 32% of all deaths[3]. In the United States, CVD resulted in 659,041 deaths in 2019. The cost of treating patients with CVD was estimated at 219 billion dollars per year in the United States[4]. Thus, it is enormously important for all clinicians to understand the factors associated with CVD and CVD mortality.

The American College of Cardiology reported that adults missing one or more teeth have a higher risk of heart disease[5]. Previous studies and systematic reviews have linked CVD with the number of missing teeth[2,6–11]. However, much heterogeneity and inconsistency in detecting and reporting disease (either CVD or missing tooth) persists in the literature[7]. Also, several studies reported a possible link between mortality due to CVD and the number of missing teeth, meaning that increased number of missing were associated with higher mortality rate due to CVD[2,12,13]. Most of the systematic reviews reported that lower number of teeth is associated with CVD and death[7,13–15], except one systematic review that reported only a marginal association[16]. There are many confounding variables when assessing the association between CVD and oral health, and some of these include diet, Body

Mass Index (BMI), total cholesterol, high density lipoprotein, blood pressure, family history of CVD, smoking, alcohol, periodontal status, levels of mediators such as C-reactive protein, fibrinogen, social/economic status factors, diet, genetics, environmental factors, and epigenetics[7,17–23].

Numerous studies have reported a strong association between tooth loss and CVD (morbidity)[13,23–27], but other studies have reported contradictory results[16,28], which means that this topic deserves further investigation. Thus, the aim of this study was to conduct an updated systematic review with meta-analysis on the impact of severe tooth loss (fewer than 10 teeth or being edentulous) on CVD mortality.

METHODOLOGY

Apriori Protocol Registration and Reporting Guidelines

The protocol of the current review was registered with the International prospective register of systematic reviews (PROSPERO; CRD42020164525). The current systematic review was reported according to the updated Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 guidelines[29].

Review Question

In patients with missing teeth compared to patients without missing teeth, what is the impact on the mortality due to CVD? In this context, "CVD" refers to course and duration of the disease if the temporality of missing teeth precedes the disease.

Search Methodology

This study adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses-S guidelines for systematic searches[30]. Unrestricted electronic searches were conducted across various databases, which included Clarivate Analytics' Web of Science, which covers Web of Science Core Collection, Korean Journal Database, Russian Science Citation Index, and SciELO Citation Index. Additionally, we searched Scopus, PubMed (including MEDLINE), and the Cochrane Central Register of Controlled Trials within the Cochrane Library. In May 2022, 2 authors (PT, AJ) independently executed the searches using a strategy developed collaboratively with a medical librarian (JJ) and the research team. Detailed search strategies for each database are available in Appendix A. These strategies underwent a rigorous peer review process, following the Peer Review of Electronic Search Strategies guideline[31]. A second information specialist provided feedback, which was incorporated into the final electronic literature search. In addition, searches were conducted for unpublished materials and grey literature in OpenGrey, Google Scholar (first 100 results), and various digital repositories (eg, Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, DART-Europe E-theses Portal, and EThOS). To ensure comprehensiveness, snowballing techniques were employed[32]. Snowballing also known as "citation searching" involves starting with a key article or reference and then identifying more recent articles that have cited the selected reference.

Reference lists from included studies and prior reviews were examined using citation indexes (Web of Science Core Collection, Scopus, and Google Scholar). Later, the searches were repeated up to December 2023, and 2 other relevant articles were added. Electronic search results were exported and subjected to duplicate removal in Rayyan[33], followed by a thorough examination of the remaining records.

Study Selection

Titles and abstracts of retrieved documents were assessed independently and in duplicate by 2 reviewers (AA, AJ). Full texts of papers that met the eligibility criteria were further independently evaluated by 2 reviewers (AA and AJ). Any disagreement was resolved by discussion.

Inclusion and Exclusion Criteria

The studies that met the following criteria were included.

1. The effect of the missing teeth on the advent of CVD mortality rate/number of missing teeth must be reported.
2. Missing teeth was defined as having fewer than 10 teeth present or being edentulous (no teeth present).
3. Studies in which the CVD outcome was defined by laboratory results and/or clinical diagnosis.
4. The effect of tooth loss on CVD mortality was measured as a primary/secondary objective.
5. The study must have had a control group with comparable or matching exposures.
6. Longitudinal cohort studies published in English language with a minimum follow-up of 3 years.

Exclusion criteria included the following: case-series, case-control studies, cross-sectional studies, or animal studies.

Data Extraction

The data extraction was performed by 2 authors (AA, AJ). Any disagreement was resolved by discussion. The followings were extracted: name of the first author, year published, type of study design, sample size, type of disease and follow-up time. The corresponding authors were contacted for clarification in case of incomplete or missing data.

Quality Assessment

The authors used Newcastle-Ottawa Quality Assessment for Cohort Studies to ascertain the quality of included studies. Thresholds and scoring for translating the Newcastle-Ottawa scales to Agency for Health Research and Quality standards were as follows (https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwi3wP-H25OEAxU-g_0HHUgOAZ4QFnoECBgQAQ&url=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2Fbooks%2FNBK115843%2Fbin%2Fappe-fm3.pdf&usg=AOvVaw3rBog32alb1VDjaGkEn_Kg&opi=89978449)[34]:

> "Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
>
> Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
>
> Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain"

Statistical Analysis

The meta-analysis considered studies in which a quantitative analysis was possible. Most of the studies used Hazard Ratio (HR) as the outcome criterion. Articles where the data for HR was not presented and/or could not be computed due to inherent differences in the data collection were excluded from meta-analyses. These HRs and their 95% CIs were logarithmically transformed (ln), and standard errors (SE) were computed from the ln-transformed 95% CIs using the formula: (ln [Upper Limit of 95% CI] - ln [Lower Limit of 95% CI])/(2 * 1.96). These transformed HR and their standard error values were used for effect size estimation. Anticipating heterogeneity, a random-effects meta-analysis, employing the restricted maximum likelihood method, was conducted to

synthesize the results, with statistical heterogeneity assessed through visual examination of confidence intervals on forest plots, complemented by the chi-square test (significance level < 10%) and I2 statistic (I2 30–60% indicating moderate heterogeneity). Subgroup analysis based on the tooth loss categories (edentulous and fewer than 10 teeth present) and a meta-regression analysis based on the number of confounders considered in each study was performed to explore potential sources of heterogeneity. In addition to the 95% confidence intervals, we calculated the 95% prediction intervals for the pooled estimates to address the potential heterogeneity and uncertainty in the effect sizes. Publication bias was evaluated using a contour-enhanced funnel plot, along with statistical tests (Egger's and Begg's) for small study effects. Seven confounders were prioritized: age, smoking, diabetes, hypertension, and BMI, Cholesterol, and Physical activity as critical in the context of CVD mortality. As a result, a subset of studies was subjected to a sensitivity analysis in which at least 5 of the critical confounding factors were accounted for, in order to determine the effect on the overall results and heterogeneity. The ln-transformed effect sizes were back-transformed into their exponential forms during the presentation of results. This step ensured the interpretability of the findings in terms of the original HRs. All the analyses were performed using STATA 18 software (StataCorp, College Station, TX).

RESULTS

Literature Search

Figure 1 presents the number of papers identified at each stage. The list of excluded articles is presented in Appendix B. Twelve articles met the inclusion criteria and were included in the systematic review as well as the meta-analysis[10,12,25,26,35–42].

Characteristics of the Included Studies

Table 1 details the characteristics of the included studies. The included studies were published from 2004 to 2023. All studies defined disease and had comparable measures for outcome of mortality rate/number due to CVD. Sample sizes ranged from 124[26] to 50,045[41]. Tooth loss was defined differently across studies, with some defining it as the loss of more than 10 teeth[12,26,35–41], or missing more than 19 teeth[10], and in some articles it was defined as edentulous[10,25,42]. All these longitudinal cohort studies used death certificate with clinical examination, or clinical data[10,12,25,26,35,36,38,39,42] or reported by physician(s) visiting the home of the family[41].

Tooth loss was reported based on survey[12,35,38,41,42], or clinical examination[10,25,26,36,39] as measurements for the number of missing teeth.

Quality of the Included Studies

The overall quality of the included studies was deemed "Good" (Appendix C). For the criteria of "comparability" studies adjusted for age, gender, smoking, social, economic status, comorbidities. However, these variables were not constant in every study.

Meta Analyses

In the primary meta-analysis involving all 12 studies, we observed a significant association between tooth loss (less than 10 teeth present or no teeth present) and CVD mortality, with an estimated HR of 1.66 (95% CI: 1.32–2.09) (Fig. 2). However, high heterogeneity was noted (I^2 = 82.42%). The test of homogeneity indicated significant variability among the studies ($P < .0001$). Sub-group analysis (Fig. 3) revealed that edentulous subgroup, comprising 7 studies[25,26,35–37,39,42], had a

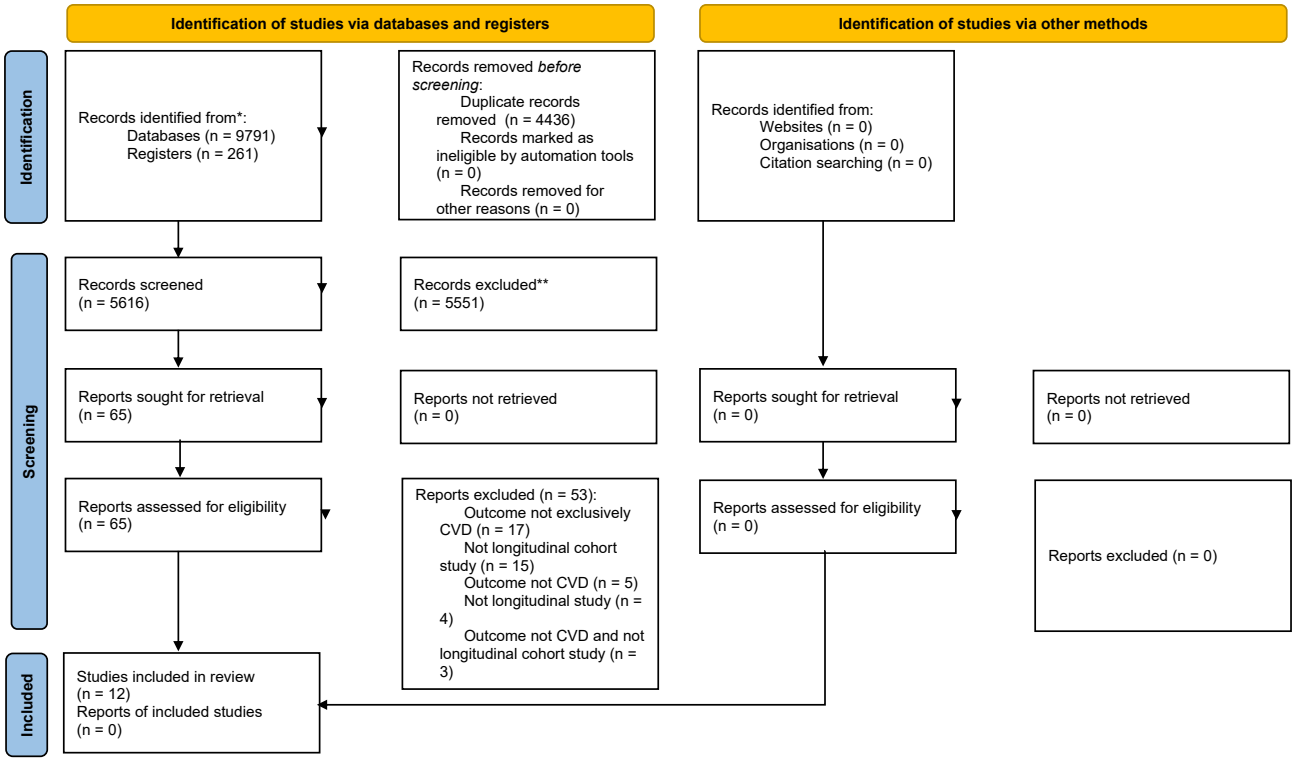

FIGURE 1 – PRISMA flowchart. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

TABLE 1 - Characteristics of Included Studies Assessing the Relationship Between Tooth Loss and CVD Mortality

No	Study	Type of record and assessment	Follow-up time	Sample size	Exposure	Control (non-missing teeth)	Representativeness	Selection	Confounders	Outcome	Source of funding
1	Ando et al 2014	Deaths from CVD (I00-I99, R96)	5.6 y	455	39 tooth loss w CVD/98 death CVD	37 non-missing teeth w CVD/98 CVD	Loss of >10 teeth increased risk of all-cause mortality	Compared with other deaths and diseases	Adjusted for age, gender, smoking, height, weight, HbA1c, education, other deaths	Tooth loss significantly increased the risk of CVD mortality for specific age group	Grant from Japanese Ministry of Health
2	Ajwani et al 2003	Defined CVD by C-reactive protein and the cut off was 3 mg/l and mortality by medical examination	10 y	364	11 loss of 10 + teeth w CVD/69 died CVD (elevated CRP)	15 non-missing and CVD/69 elevated CRP	Loss of >10 teeth increased risk of all-cause mortality	Compared with other deaths and diseases	Adjusted for age, gender, smoking, height, weight, HbA1c, other deaths	Tooth loss significantly increased C-Reactive Protein but not CVD mortality	Ragnar Ekberg Foundation, Center for International Mobility, Päivikki and Sakari Sohlberg Foundation
3	Bond et al 2022	Defined by International Statistical Classification of Disease	49 y	2280	Loss of all teeth with CVD 21/2810 capturing edentulous person-time (not recording one time assessment)	Non-edentulous and CVD 122/38,107	Loss of all teeth	Compared to all-cause mortality, cardiovascular disease mortality	Stratified and adjusted for confounding variables such as smoking, income, education	After regression analysis, there was a positive association between tooth loss and CVD mortality	US Department of Veteran Affairs
4	Dai et al 2023	Chinese Longitudinal Healthy Longevity Survey	3.1 y	5403	60% mortality missing more than 10 teeth	13.2% mortality having 20+ teeth	Missing more than 10 teeth		Adjusted age, gender, marital status, smoking, drinking, education, heart disease, respiratory, obesity, BMI, diabetes, cancer, eating habits	Missing more than 10 teeth is linked to an increased risk of CVD mortality	Jiangxi Provincial Health Commission
5	Gato et al 2020	Death certificates	11 y	11,273	78/6174 + 65/4/2478	77/2621	Loss of >10 teeth	Compared with other deaths and diseases like cancer	Adjusted for age and sex	Multivariate analysis showed number of missing teeth associated with increased risk of CVD mortality	Ministry of Education
6	Holmlund et al 2010	The international classification of disease and related health problems (ICD) was used to classify the fatal and non-fatal CVD diagnoses	12 y	7674	Hazard Ratio = 4.63	Hazard Ratio = 1.06	Missing more than 7 teeth (remaining more than 25 teeth)	Cox proportional hazard adjusted for periodontal disease and it did not predict CVD	Did not adjust for diabetes, lipids, blood pressure, age, gender and smoking	Multivariate analysis showed number of missing teeth associated with increased risk of CVD mortality	Research and development Centre
7	Janket et al 2014	Finish Death Registry	15 y	124	35/117; each increment of 10 teeth increased mortality by 27%	11/167	Missing more than 10 teeth	Adjusted for age, sex, smoking, hypertension, DM, cholesterol ratio, education, CRP	Multivariate hazard models	Adjusted for hazard models, multivariate analysis showed number of missing teeth were associated with increased risk of CVD mortality	Intramural Research Program of the National Cancer Institute
8	Liu et al 2022	Data from National Health and Nutrition Examination Survey	27 y	5270	Missing all the teeth 277	Remaining 25–28 teeth 226	10 teeth missing	Age, sex, race, income, education, insurance, BMI, physical activity, smoking	Adjusted regression model	Loss of teeth was associated with CVD mortality	National Institutes of Health
9	Shen et al 2023	Data from National Health and Nutrition Examination Survey 1999–2014	10 y	2152	Missing more than 10 teeth		Missing more than 10 teeth	Age, sex, ethnicity, income, education, smoking, alcohol, healthy eating, BMI, hypertension, diabetes, CVD, kidney disease, cancer,	Adjusted regression models	Loss of teeth was associated with mortality but the risk did not increase after age 65 y	Zhejiang Traditional Chinese Medicine Research

(*continued on next page*)

TABLE 1 - Continued

No	Study	Type of record and assessment	Follow-up time	Sample size	Exposure	Control (non-missing teeth)	Representativeness	Selection	Confounders	Outcome	Source of funding
								periodontal disease, medications			
10	Vogtmann et al 2017	Participants were contacted and when death was reported, a physician visited the home of the family or primary care givers and conducted verbal autopsy	4 y	50,045	more teeth missing than expected hazard ratio 1.33 (1.13–1.56)	fewer teeth missing than expected Reference 1	Unclear	Adjusted for age, gender, income, education, ethnicity, smoking, frequency of brushing	Didn't adjust for models	Poor oral health was a predictive value for CVD mortality	Intramural Research Program of the National Cancer Institute
11	Watt et al 2012	Patient-based database contained information on mortality. Classification of cause of death was based on death certificate	8.3 y	1287	Edentate	No missing tooth	Missing all teeth	Adjusted for demographic, socio-economic, health status	Cox regression analysis	Edentate was a significant predictor for CVD mortality	No Funding
12	Yu et al 2021	Death certificates from the National Death Index	72.6 mo–96.92 mo, 6–8 y	3978	Missing more than 19 teeth (number of teeth 0–9)- CVD 21.4% (994)	20–28 teeth- CVD 4.7% (1175)	Missing all teeth of having only 9 teeth	Adjusted for age, gender, race, education, income, BMI, smoking, physical activity, existing medical conditions	Cox hazard survival analysis	Fewer number of teeth was associated with CVD mortality	National Institute of Health

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive Protein; CVD, cardiovascular disease; DM, diabetes mellitus.

pooled hazard ratio (HR) of 1.534 [95% CI: 1.322–1.779], indicating a 53.4% higher risk with no significant heterogeneity (I^2 = 0.00%). The 95% prediction interval for this subgroup was 1.263 to 1.863. The subgroup with fewer than 10 teeth, comprising 5 studies[10,12,38,40,41], had a pooled HR of 1.825 [95% CI: 1.074–3.101], suggesting an 82.5% higher risk but with substantial heterogeneity (I^2 = 94.93%). The 95% prediction interval for this subgroup was 0.238 to 13.997. The test for subgroup differences was not statistically significant (Q = 0.38, P = .536), indicating similar risk levels between the 2 conditions. The 95% prediction interval for all the 12 included studies was 0.729–3.779.

Furthermore, meta-regression analysis explored the potential influence of the number of confounders considered in each study on the observed associations (each study considered varying number of confounders ranging from 3 to 23 confounders). This analysis did not reveal any impact on the estimate or heterogeneity (P = .626, I^2 = 83.7), suggesting that variations in the number of confounders across studies did not affect the overall findings.

Publication Bias

Publication bias assessments, including Egger and Begg's tests, did not indicate significant small-study effects or publication bias (Fig. 4).

Sensitivity Analysis

Though age and smoking were considered in all the 12 studies, 2 studies[12,41] omitted 5 critical confounding variables namely diabetes, hypertension, BMI, Cholesterol and Physical Activity. In the sensitivity analysis (Fig. 5) of ten studies (excluding Holmlund et al and Vogtmann et al)[12,41], the summary estimate remained significant (HR = 1.52, 95% CI: 1.28–1.80) with 95% prediction interval of 0.947–2.445, and the heterogeneity was notably reduced (I^2 = 51.82%), confirming the impact of tooth loss on CVD mortality.

DISCUSSION

This systematic review of longitudinal studies with meta-analysis reported that having less than 10 teeth or less significantly increases the risk of CVD mortality. Many studies in cardiovascular medicine consider 3-year follow-up an appropriate long-term recall[43–47]. For the reasons of consistency, the authors only used longitudinal cohort studies with a minimum follow-up of 3 years. The range of follow-up was from 3.1 years[37] to 49 years[25]. Age and smoking were considered in all the articles. Seven confounders were prioritized: age, smoking, diabetes, hypertension, BMI,

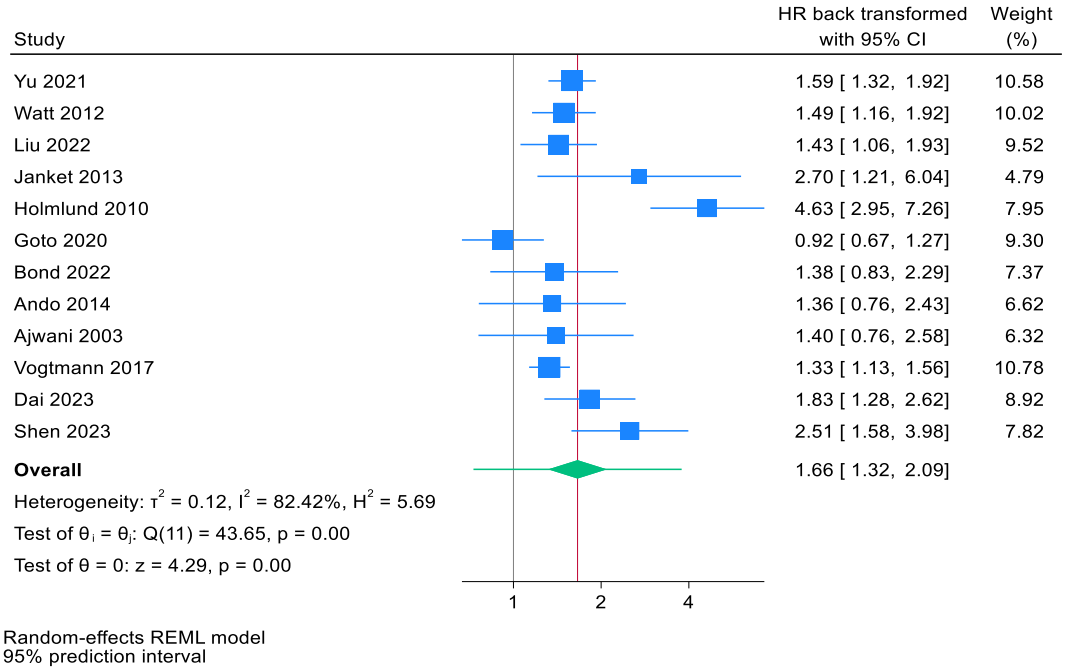

FIGURE 2 – Primary meta-analysis (Note: In the Janket et al study, HRs and 95% CIs were inverted, as the reference category used in their model was edentulous teeth which is in contrast with remaining 11 studies; 95% prediction interval: [0.729, 3.779]).

Cholesterol and Physical activity as critical in the context of CVD mortality. All the articles but two[12,41] adjusted for at least 5 of these critical confounders (diabetes, hypertension, BMI, Cholesterol and Physical Activity). When stratifying the data into sensitivity analysis on the subset of studies which considered at least 5 critical confounders, to assess the impact on the overall findings and heterogeneity, patients with less than 10 remaining teeth or edentulous had an increased risk of the CVD mortality, confirming the impact between tooth

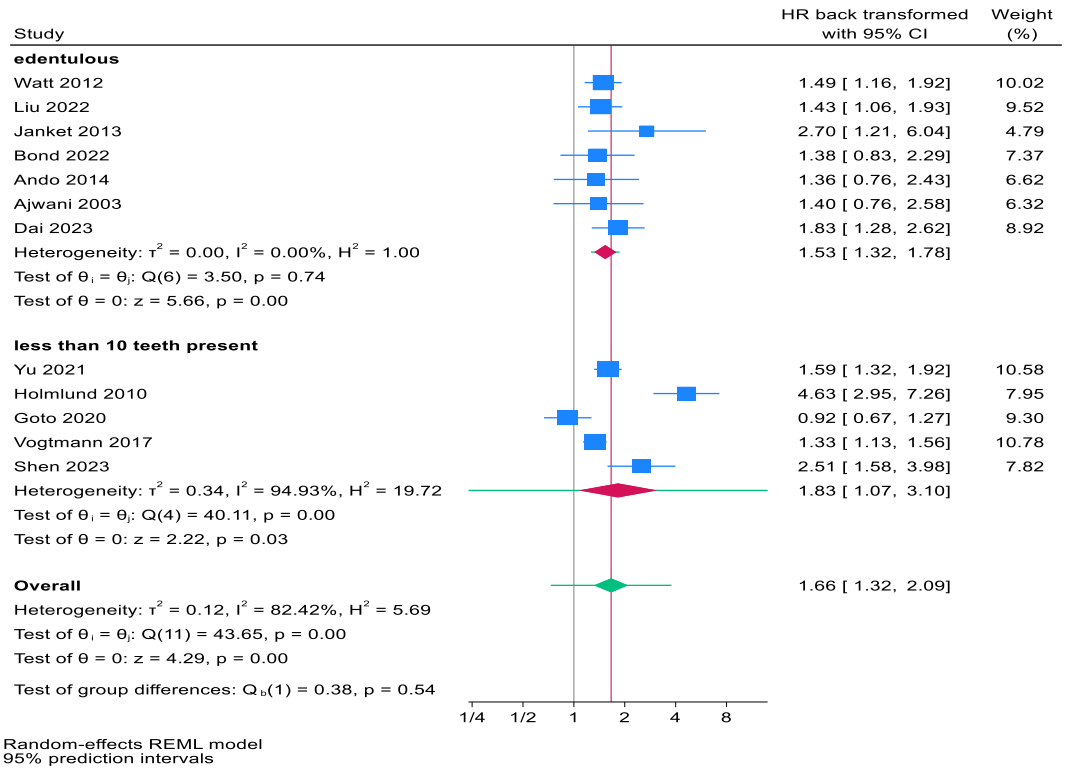

FIGURE 3 – Sub-group analysis (95% prediction interval for the sub-groups: edentulous [1.263, 1.863], less than 10 teeth present [0.238, 13.997]).

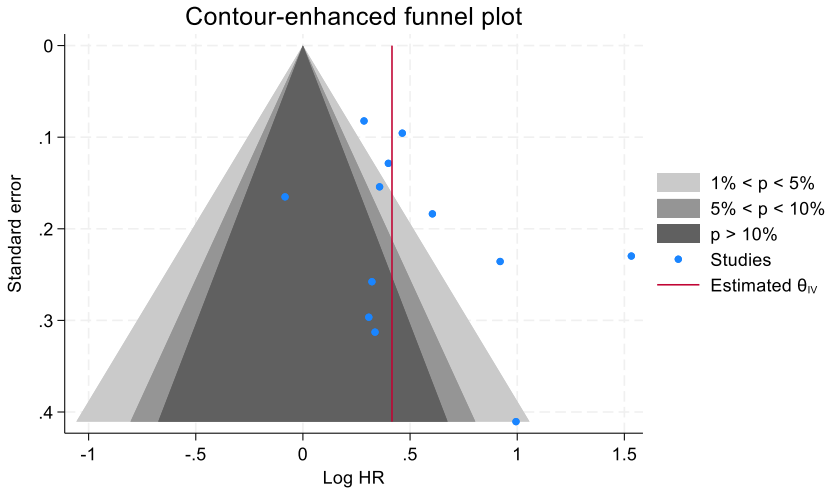

FIGURE 4 – Publication bias.

loss and CVD mortality. Moreover, the 95% prediction intervals provide an estimate of the range within which the true hazard ratio (HR) for a future study is expected to fall. In cases of high heterogeneity, such as observed in this meta-analysis, the importance of 95% prediction intervals becomes paramount as they provide valuable insights into the potential variability and uncertainty of effect sizes in future studies, thereby aiding in the interpretation of the overall findings. It is worth noting that the current systematic review did not assess the association between CVD morbidity and tooth loss.

The financial burden of death due to CVD was estimated to be $147 billion in lost productivity on the job in 2018 in the US[48]. By 2035, >130 million adults in the US population (45.1%) were projected to have some form of CVD, and total costs of CVD, morbidity and mortality combined, were expected to reach $1.1 trillion in 2035[49]. One way to reduce these figures, based on the findings of this systematic review, is to increase public awareness as well as clinician's awareness about the value of saving natural teeth.

Biological plausibility supporting this concept of missing teeth and CVD mortality at this time is conjectural and multifactorial, but previous studies have reported on inflammatory bioburdens[50], pocket depths[51], diet[52], microbiome[53,54], dose-response effect of tooth loss[13,16] as possible indicators for CVD mortality. In part it can be deducted that perhaps with chronic infection resulting in tooth loss the damage has already taken place. Another possible explanation could be that tooth loss does not indicate absence of infection and as such the function of teeth and the periodontium in protecting the oral cavity from microbial invasion and risk of mortalities should be further investigated[36]. It is possible that teeth and periodontal structure have a protective mechanism in the oral/systemic health in such a way that tooth loss becomes a risk factor for CVD mortality as it enables easier access for microbes through damaged tissue. The authors infer that based on the context described above, teeth function as anatomical barrier and should perhaps be included as part of the overall defense mechanism.

However, the search for this goal remains unfulfilled. These findings indirectly support the concept of saving teeth through endodontic treatments to reduce the risk of CVD mortality and are indirectly consistent with a previous study that reported lower risk of CVD mortality in patients who had endodontically treated teeth[55]. The authors speculated that endodontic treatments may reduce bioburden, inflammatory burden, production of immunologic cells, cytokines and chemokines which would overall increase the risk of atherosclerosis and CVD mortality[55]. Thus, saving teeth and keeping an optimal oral health cannot be underestimated.

The findings of the current review contribute indirectly to the concept of tooth

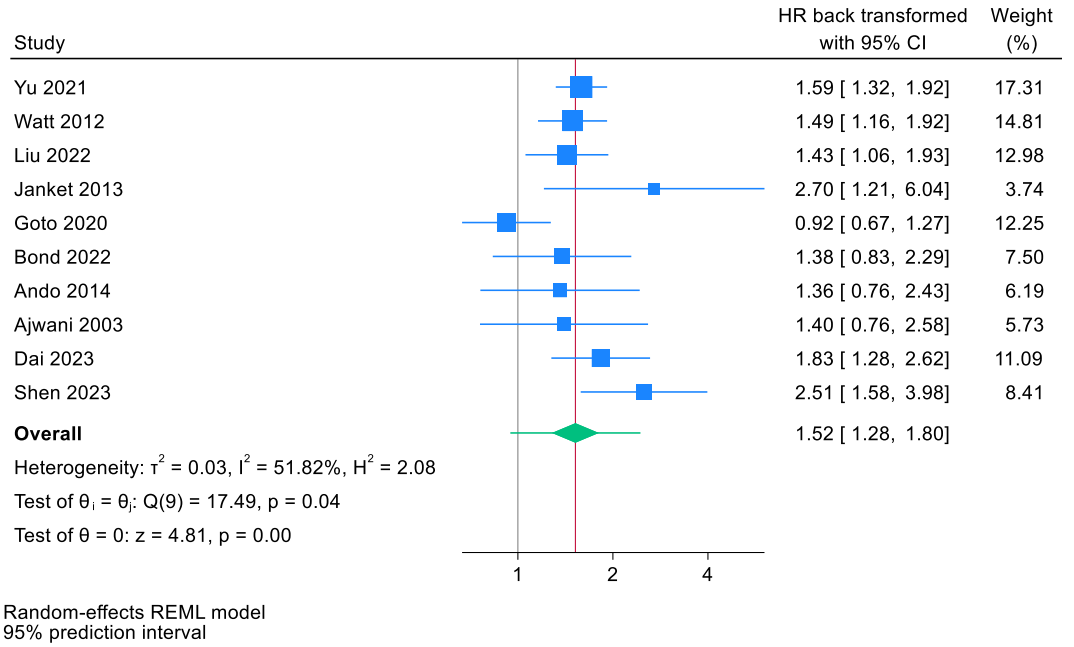

FIGURE 5 – Forest plot (Sensitivity analysis based on the studies which considered at-least 5 out of 7 essential confounding factors; 95% prediction interval: [0.947, 2.445]).

preservation. Although saving teeth through endodontic treatment was not the subject of this review, it seems logical to conclude that this conceptual gap merits considerable attention. As oral health and CVD are not unique topics, this systematic review also reveals that there is a need for methodological standardization for this type of important research. It has been hypothesized that chronic inflammation and poor diet are pathways linking missing teeth and CVD mortality[6,13,56]. Periodontal disease as a confounding variable has been reported to be associated with CVD mortality[57,58]. These types of research studies can aid in predicting the incidence of CVD mortality[59]. The other question is studying cost and benefit of keeping dentition on the overall systemic health. These questions deserve further attention.

The current review used Newcastle-Ottawa Quality Assessment for Cohort Studies to appraise the quality of included studies. The overall quality of the included studies was "good". The lack of blinding in the outcome assessment of the included studies might be attributed to the inherent nature of the research.

There are several limitations to this systematic review such as heterogeneity among the included studies, reporting different numbers of missing teeth, not reporting on other systemic diseases, genetic predisposition and variation in the assessment of proportional hazard's assumption across the primary studies included in our meta-analysis. Five studies[26,35,39,41,42] tested this assumption using Schoenfeld residuals, time-interaction variables, or survival curves. One study[25] did not verify the assumption explicitly due to the use of time-varying covariates, which inherently introduce nonproportional hazards. Five studies[10,12,36–38] did not test the assumption, although two[12,37] of which provided survival curves and we visually assessed it to assume proportionality. One study[40] assessed non-linear relationships using a multivariable Cox model with restricted cubic splines. This lack of assumption assessment and the time varying co-variates in the above-mentioned studies may introduce uncertainty in the constancy of hazard ratios over time. Future primary studies should include detailed data (such as results of assumption tests, Schoenfeld residuals, Survival Curves, and incorporating time-varying coefficients or interactions to allow for nonproportional hazards in the model) to facilitate better assessment of the estimates. Considering the above said limitations, causal inference cannot be definitively deducted. As to the question why this association would be present long after the infection is removed or the tooth extracted, leaves more questions for the future studies[25].

A number of studies and systematic reviews have reported on the risk of tooth loss and mortality due to all causes[7,16,60,61], but 1 systematic review that was published in 2019 reported inconsistent results on the risk of tooth loss and CVD mortality[16]. This systematic review reported that tooth loss above 10 missing teeth was marginally statistically significant with the risk of CVD mortality[16]. However, when the authors adjusted for confounders such as age, smoking, alcohol, physical activity, BMI, socioeconomic status, marital status, missing teeth was associated with CVD mortality. On the other hand, when adjusted for diabetes and hypertension, missing teeth was not statistically associated with CVD mortality. In the present study, controlling for confounders did not change the outcomes.

CONCLUSION

The present systematic review reported that being edentulous or having less than 10 teeth is significantly associated with CVD mortality. Future longitudinal studies should include large sample sizes and control for genetic predisposition, diet, oral hygiene, medication, comorbidities, physical activity, and should delineate the confounding variables. Moreover, the importance of cost, risks, and benefits of preventing CVD mortality through saving teeth via endodontic treatments should be better investigated.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at www.jendodon.com (https://doi:10.1016/j.joen.2024.06.012).

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