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Does-response meta-analysis on tooth loss with the risk of cognitive impairment and dementia

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Abstract

Objectives: To quantify the dose-response associations between tooth loss and risk of cognitive impairment and dementia.

Design: Longitudinal studies that examined the association between tooth loss and cognitive function were systematically searched on six databases through March 1, 2020. The study adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. Risk estimates were pooled using random-effects models. The dose-response associations were assessed using generalized least squares spline models.

Setting and Participants: Adults from community, institution, out-patient or in-hospital were included in the meta-analysis.

Measures: Cognitive impairment and dementia were defined by neuropsychological tests, diagnostic criteria, or medical records. Tooth loss was self-reported or assessed by clinical examinations.

Results: Fourteen studies were entered into the meta-analysis, including 34,074 participants and 4,689 cases with diminished cognitive function. Participants with more tooth loss had a 1.48

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Authors contribution

Xiang Qi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Bei Wu. Acquisition, analysis, and interpretation of data: Xiang Qi and Zheng Zhu. Drafting of the manuscript: Xiang Qi. Critical revision of the manuscript for important intellectual content: Brenda L. Plassman, Bei Wu. Statistical analysis: Xiang Qi. Obtained funding: Bei Wu. Supervision: Bei Wu.

Disclosure statement

None of the authors stated a conflict of interest.

times higher risk of developing cognitive impairment (95% CI = 1.18–1.87) and 1.28 times higher risk of being diagnosed with dementia (95% CI = 1.09–1.49). However, the association was non-significant for participants using dentures (RR = 1.10, 95% CI = 0.90–1.11). Eight studies were included in the dose-response analysis, and data supported the use of linear models. Each additional tooth loss was associated with a 0.014 increased relative risk of cognitive impairment and 0.011 elevated relative risks of dementia. Edentulous participants faced a 1.54 times higher risk of cognitive impairment and a 1.40 times higher risk of being diagnosed with dementia.

Conclusions and Implications: Moderate-quality evidence suggested tooth loss was independently associated with cognitive impairment and dementia; risk of diminished cognitive function increased with incremental numbers of teeth lost. Furthermore, timely prosthodontic treatment with dentures may reduce the progression of cognitive decline related to tooth loss.

Summary

A meta-analysis examining a dose-response association between tooth loss and risk of cognitive impairment and dementia was performed. We found each additional tooth lost was associated with a 0.014 increased relative risk of cognitive impairment and a 0.011 elevated relative risk of dementia.

Keywords

oral health; cognitive decline; meta-analysis; systematic review

Introduction

Alzheimer’s disease and related dementia is one of the leading causes of mortality in the world.[1] It has been estimated that about 50 million people world wide had dementia in 2019, and it is estimated that this number will triple by 2050.[2] Mild cognitive impairment (MCI) represents a transitional stage between normal and age-related cognitive decline and dementia, during which early detection and intervention may be possible.[3–5] Identifying individuals at risk for diminished cognitive function is, therefore, essential for planning strategies to prevent the onset and progression of dementia.

Compared to younger age groups, older individuals suffer from disproportionately poorer oral health, including a higher number of teeth lost, dental caries, and a higher prevalence of periodontitis.[6] Cognitive impairment may serve as a major contributing factor. Individuals with cognitive impairment have a greater functional dependency. They are often reliant on others for their daily oral care, and thus are more likely to have deficient oral hygiene, more periodontal disease, and greater tooth loss.[7] Among the increasing number of cognitively impaired residents in long-term care facilities, the need for regular good oral hygiene care is further accentuated.[8] Combined these findings have led to increasing attention being devoted to understanding the association between tooth loss and diminished cognitive function.[9–15]

To our knowledge, five meta-analyses[9,11–13,16] have been conducted to examine tooth loss and cognitive impairment. However, the conclusions from some systematic reviews were mixed,[14–16] resulting in unanswered questions on whether an association exists, underlining the issue of the methodological quality from their synthesized evidence. First,

the determination of incident dementia is inaccurate for those meta-analyses that included cross-sectional studies.[11,13] Second, two meta-analyses[13,16] did not present the quality appraisal of evidence using structured tools, leading to bias in reporting the synthesized result. Third, the level of cognitive and functional impairment differs between dementia and MCI or other forms of mild impairment; however, four meta-analyses failed to analyze cognitive impairment and dementia separately.[11–13,16]

Recently, a few studies have been conducted to examine tooth loss and the risk of cognitive impairment and/or dementia using longitudinal cohort data.[17–19] We, therefore, conducted a meta-analysis using longitudinal studies, aiming to provide contemporary evidence investigating a dose-response association between tooth loss and the risk of cognitive impairment and dementia.

Methods

Protocol and Registration

This meta-analysis protocol was registered in the National Institute for Health Research, International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42019128023). The reporting of this study was in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guideline (Appendix S1).[20]

Search Strategy—We searched six databases, including PubMed/MEDLINE, Medline (Ovid), EMBASE (Ovid), CINAHL (EBSCO), Web of Science, and Cochrane Library (Wiley) up to March 1, 2020. A search strategy was developed for each database using a combination of free text and controlled vocabulary terms (Appendix S2). The reference lists of included studies were also screened as a supplement to searching the databases.

Study Selection—Inclusion criteria were: 1) longitudinal studies that examined the association between tooth loss and cognitive impairment or dementia; 2) the exposure was tooth loss, and the outcome was cognitive impairment/decline, or any types of dementia/Alzheimer's disease; 3) with empirical data as follows: beta-coefficient (β), odds ratio (OR), relative risk (RR), hazard ratio (HR) with 95% confidence interval (CI)/standard error (SE) or enough information for calculating β, OR, RR or HR; 4) published in peer-reviewed English language journals. Any type of setting, including but not limited to community, institution, out-patient or in-hospital, were eligible. Exclusion criteria: articles that only included children and adolescents. Considering duplicates and studies reporting on the same cohort, we only kept the latest publication or the study with the larger sample size, longer follow-up period, and with more confounders adjusted. Titles and abstracts were screened against inclusion and exclusion criteria. The full texts of selected studies were assessed by two independent reviewers (First and second author). Any conflicts between the reviewers were resolved by a third reviewer (Forth author).

Data Extraction and Quality Assessment—Two reviewers independently (First and the second author) extracted information from articles, including authors, publication year, geographic region, study design, study setting, sample demographics (age, gender), follow-up period, tooth loss measures and cognitive assessment, adjustment for covariates,

and main findings. Discrepancies were solved through group discussion. We applied the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies to assess the risks of bias. Assessment tools were selected in accordance with the study designs encountered. One point was assigned for the presence of a quality feature, with scores ranging from 1–9.[21] Studies with NOS scores of 1–3 were defined as poor quality, 4–6 intermediate, and 7–9 high. The quality of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[22]

Statistical Analysis—We examined the association between tooth loss and cognitive impairment or dementia through pooling RRs and corresponding 95% CIs for the highest risk vs. the lowest risk. RR was regarded as equivalent to HR and OR as there is a low prevalence of cognitive impairment and dementia in the combined sample of this study all populations (i.e., < 20%).[23] We used random-effects meta-analysis and quantified heterogeneity among studies using the Q test and I^2 statistic. Additionally, subgroup analysis and meta-regression were performed to explore the source of heterogeneity. The possibility of publication bias was evaluated using the Begg rank correlation test and the Egger linear regression test.

Dose-response analyses were performed using the method described by Greenland and Longnecker.[24] Only studies with at least three quantitative categories of tooth loss were included. We assigned the median level of numbers of teeth lost in each category to the corresponding RRs. If the highest or lowest categories were open-ended, we set the highest boundary to 32 teeth intact (unless specified) and the lowest boundary to complete edentulous. We applied a restricted cubic spline model with 3 knots at 10th, 50th, and 90th percentiles to evaluate the potential non-linear relationship.[25] The linear and non-linear models were also compared by using a two-stage random-effects model. Results were considered significant at two-tailed $P < 0.05$. All data analyses were conducted using Stata 15.1 software (Stata Corp, College Station, TX).

Results

Literature Search

Fourteen studies were identified in this review. The study selection process and the literature search results are depicted in Appendix S3. Among the 14 articles, three articles conducted separate analyses on either education level (higher and lower),[26] cognitive function (cognitive impairment and dementia),[27] or gender (male and female);[28] therefore, the final meta-analysis contained 17 datasets. Eight studies were included in the dose-response analysis.[27–34]

Assessment of Tooth Loss

All included studies evaluated tooth loss as exposure of interest. The number of teeth lost was assessed through clinical examinations in nine studies[18,19,26,29–33,35] and from the self-reported number of teeth lost in five studies.[3,17,27,28,34]

Assessment of Cognitive Impairment and Dementia

Incident dementia was the cognitive outcome in eight studies.[3,26,28,31–35] The diagnosis of dementia was based on Diagnostic and Statistical Manual of Mental Disorders, third edition revised/fourth edition (DSM-III R/IV) in four studies,[26,32,33,35] medical records and death certificates in two studies,[3,28] data from a long term care insurance database that included in-person standardized questionnaires reviewed by a group of clinicians,[34] or assessment of cognitive and functional ability using standardized measures including a battery of neuropsychological tests.[31] In five studies, the reported outcome was the incidence of cognitive impairment.[17–19,29,30] Mini-Mental State Examination (MMSE) or a single MMSE item was the most common measurement in four studies,[17,19,29,31] followed by the Japanese version of the Montreal Cognitive Assessment.[18] One study[27] reported both the measurement of cognitive impairment and dementia, DSM-IV was used to diagnose dementia, and cognitive impairment was measured by MMSE.

Selected Studies and Characteristics

Detailed characteristics of the included studies were shown in Appendix S4. Nine were prospective[17–19,26,27,29,30,33,34] and three were retrospective cohort studies,[28,31,32] and two were case-control nested in cohort studies[3,35]. Six studies were conducted in Japan,[18,19,29,30,33,34] followed by the US (three),[28,31,32] Sweden (two),[3,17] France (one),[26] Korea (one),[35] and UK (one).[27] All studies were conducted among community-dwelling older adults, except one which was from an institutional setting[30]. The sample sizes of studies varied from 14[19] to 11,140.[27] The average age of participants ranged from 65.8[27] to 84.[31]

Risk of Bias

The overview of the quality appraisal of included studies is presented in Appendix S5. Five cohorts were followed for more than 10 years,[26,28,31,32,35] while four studies less than 5 years.[18,31,34,35] The mean quality score of the included studies is 7.6 ± 1.3. For 12 cohort studies, the results showed the methodological deficiency was that attrition was not accounted for in the follow-up cohort,[18,19,27] and tooth loss was self-reported in five of the studies.[3,17,27,28,34] Four studies did not control the participants' age or gender.[18,26,28,34] Two studies were conducted on females only.[31,32] The two nested case-control studies failed to provide the information on the non-response rate.[3,35]

Association Between Tooth Loss and Risk of Cognitive Impairment and Dementia

Six studies[17–19,27,29,30] compared the incidence of cognitive impairment between subjects with more teeth lost versus fewer teeth lost. The pooled adjusted RR revealed that participants with more teeth lost had 1.48 times higher risk of developing impairment (95% CI = 1.18–1.87) compared with fewer teeth lost (Figure 1A). Nine studies examined the association between tooth loss and incident dementia.[3,26–28,31–35] Participants with more teeth lost had 1.28 times higher risk of being diagnosed with dementia (95% CI = 1.09–1.49) (Figure 1B).

Linear Dose-Responses Association Analysis

The analysis investigating the dose-response relationship between tooth loss and cognitive impairment was based on three studies (Figure 2A).[27,29,30] A linear relationship was detected ($P = 0.81$ for non-linearity), and the analysis suggested that every missing tooth increased the relative risk of cognitive impairment by 1.01 times (95% CI = 1.01–1.02). The risk increased to 1.31 times when the number of missing teeth went up to 20 (95% CI = 1.20–1.43). Edentulous participants faced 1.54 times higher risk of cognitive impairment (95% CI = 1.34–1.78). We examined the dose-response relationship between tooth loss and dementia using six studies.[27,28,31–34] No evidence of nonlinearities was observed ($P = 0.70$ for non-linearity). Each additional tooth loss was associated with a 1.01 higher dementia relative risk (95% CI = 1.00–1.02) (Figure 2B). Accordingly, edentulous participants faced a 1.40 times higher risk of dementia (95% CI = 1.10–1.80).

Subgroup Analysis and Meta-Regression

To confirm the robustness of our study findings, we conducted subgroup analysis and meta-regression on possible sources of heterogeneity.

Our subgroup analysis revealed that the association between tooth loss and the risk of diminished cognitive function was not substantially changed by study design, study setting, geographic region, sample size, follow-up period, self-reported vs. clinically examined tooth loss, and score quality (Table 1). However, significant differences were detected when stratified by denture status. Ten datasets obtained from four publications were used to analyze the risk of cognitive decline among tooth loss participants with and without dentures.[28,30,34,35] The result showed a distinct association for the without-denture group only (with denture: RR = 1.00, 95% CI = 0.90–1.11; without denture: RR = 1.55, 95% CI = 1.24–1.94).

The results of multivariate meta-regression showed that study design, study setting, geographic region, sample size, follow-up period, self-reported vs. clinically examined tooth loss, age, gender, adjustment for covariates, and score quality did not affect the risk of cognitive decline (all $P > 0.1$).

Publication Bias

The symmetry in Appendix S6 in the supplement is not perfect when the outcome is cognitive impairment, but still implied the absence of significant publication bias, which was confirmed by Egger's test ($P = 0.13$) and Begg rank correlation test ($P = 0.19$). The funnel plot is symmetrical when the outcome is dementia (Appendix S6). We did not observe significant publication biases in our included studies, neither in Begg rank correlation test ($P = 0.81$) nor in Egger's linear regression test ($P = 0.94$).

Quality of Evidence

The quality of the evidence was moderate for the associations owing to the presence of dose-response gradients. Despite that the quality of evidence started from "low" because the included studies were all observational,[22] the dose-response gradient upgrades the quality of evidence for the two outcomes by one level (Table 2).

Discussion

This meta-analysis revealed the association between tooth loss and risk of cognitive impairment and dementia based on 14 longitudinal studies containing 34,074 participants and 4,689 cases with diminished cognitive function. Our results indicated that more tooth loss increased the risk of cognitive impairment by 1.48 times and dementia by 1.28 times, even after controlling for a range of potential confounders. A further dose-response analysis detected linear associations between tooth loss and cognitive impairment or dementia, suggesting that the more teeth missing, the higher risk of cognitive impairment and dementia. In subgroup analysis and meta-regression, we found that the association between tooth loss and cognitive impairment was affected by denture status. The quality of evidence was “moderate” for the association between tooth loss and cognitive impairment and dementia owing to the dose-response gradients.[22]

We also detected a higher incidence of cognitive impairment or dementia among 3,567 edentulous participants without dentures (23.8%) compared to those with dentures (16.9%). The differential risks of cognitive impairment/dementia based on denture status may be explained by the alteration of chewing ability.[28,30,34,35] A recent large-scale cohort study on Chinese older adults found that denture use attenuated the detrimental effects of tooth loss, especially for partial tooth loss, on cognitive impairment.[36] The putative protective effect of denture use on cognitive impairment was also demonstrated in a few population-based studies.[37,38] For instance, cross-sectional studies suggested that both the retention of natural teeth and the rehabilitation of the missing teeth[37] with prostheses such as dentures and guaranteeing functional denture quality[38] could attenuate cognitive impairment.

Multiple explanations have been offered for the association between tooth loss and diminished cognitive function. Consistent with the apparent benefit of denture use, some have proposed that masticatory dysfunction after tooth loss may promote morphologic or cholinergic changes in specific brain regions related to cognition.[39–42] Another possible explanation is that tooth loss and suboptimal masticatory function contribute to nutritional deficiencies leading to loss of key nutrients for brain health. For example, Vitamin D has been reported to inhibit the activity of certain cytokines related to periodontal disease and dementia by reducing the expression of interleukin-6, interleukin-8, and tumor necrosis factor-α.[43,44] Finally, the proposed role of oral inflammation and pathogenic oral bacteria, such as *Porphyromonas gingivalis,* on neuroinflammatory processes and beta-amyloid production has received increasing attention as a possible mechanism.[45–47] Periodontitis, an etiological factor of tooth loss, also stimulates the release of inflammatory cytokines which are related to the activation of molecules contributing to the progression of dementia, such as C-reactive protein, tumor necrosis factor-α, immunoglobulin G, interleukin-1β, and interleukin-6.[48–50]

Despite the numerous posited mechanisms for the association between tooth loss and dementia,[51] none of them have yet gained sufficient empirical support. Tooth loss may also reflect life-long socioeconomic disadvantages, such as limited access to and quality of medical and dental care, fewer years of education, and poor nutrition. Some of these factors are themselves associated with a greater risk of cognitive impairment in later life.[52,53] In

addition, we cannot exclude the possibility of reverse causality being the explanation for our findings. Previous cohort studies founded that cognitive decline was associated with infrequent toothbrushing, plaque deposit, and increased odds of edentulism.[54,55] Cognitive impairment may increase the risk of tooth loss due to poor oral hygiene among people living with dementia.[7]

The strengths of this meta-analysis lie in several aspects. First, our study targeted longitudinal studies, which may reduce the sampling error and recall bias.[56] In addition, we found a dose-response association between tooth number and risk of diminished cognitive function, thus substantially strengthening the evidence linking tooth loss to cognitive impairment and providing some evidence for a causal association.[24] The subgroup analysis and meta-regression also were conducted to clarify possible confounders affecting the result. Evaluation of publication bias indicated that it did not impact the final results. We thus conclude that tooth loss is associated with the risk of incident cognitive impairment and can be regarded as a risk factor for cognitive impairment and dementia.

Limitations

Limitations of this study need to be acknowledged. First, although the longitudinal design allows us to comment on the direction of the association between tooth loss and cognitive decline, heterogeneity across different studies still exists, such as the different methodological approaches and range of indicators used to assess cognitive function. Second, we should be cautious when interpreting the synthesized results since three of the cohort studies did not report the attrition rate. Third, the NOS tool's decision rules are vague, difficult to use, and of questionable reliability in observational studies.[57] In our meta-analysis, the NOS rating criteria for the outcome (cognitive assessment in cohort studies) did not allow for capturing the variety of factors that influence the validity of the cognitive outcome, which might lead to an underestimated risk of bias of the included studies.

Conclusions and Implications

In summary, this study provided further support of tooth loss as a risk factor for cognitive impairment and dementia. Furthermore, this review highlights that maintaining good oral health may help preserve cognitive function. The findings also indicate that timely prosthodontic treatment may slow the progression of cognitive decline. In clinical practice, health professionals can play an important role in educating patients and family members on the importance of improving oral health. Implementation of population-based oral health promotion programs and interventions have the potential to benefit a range of health issues, including cognitive health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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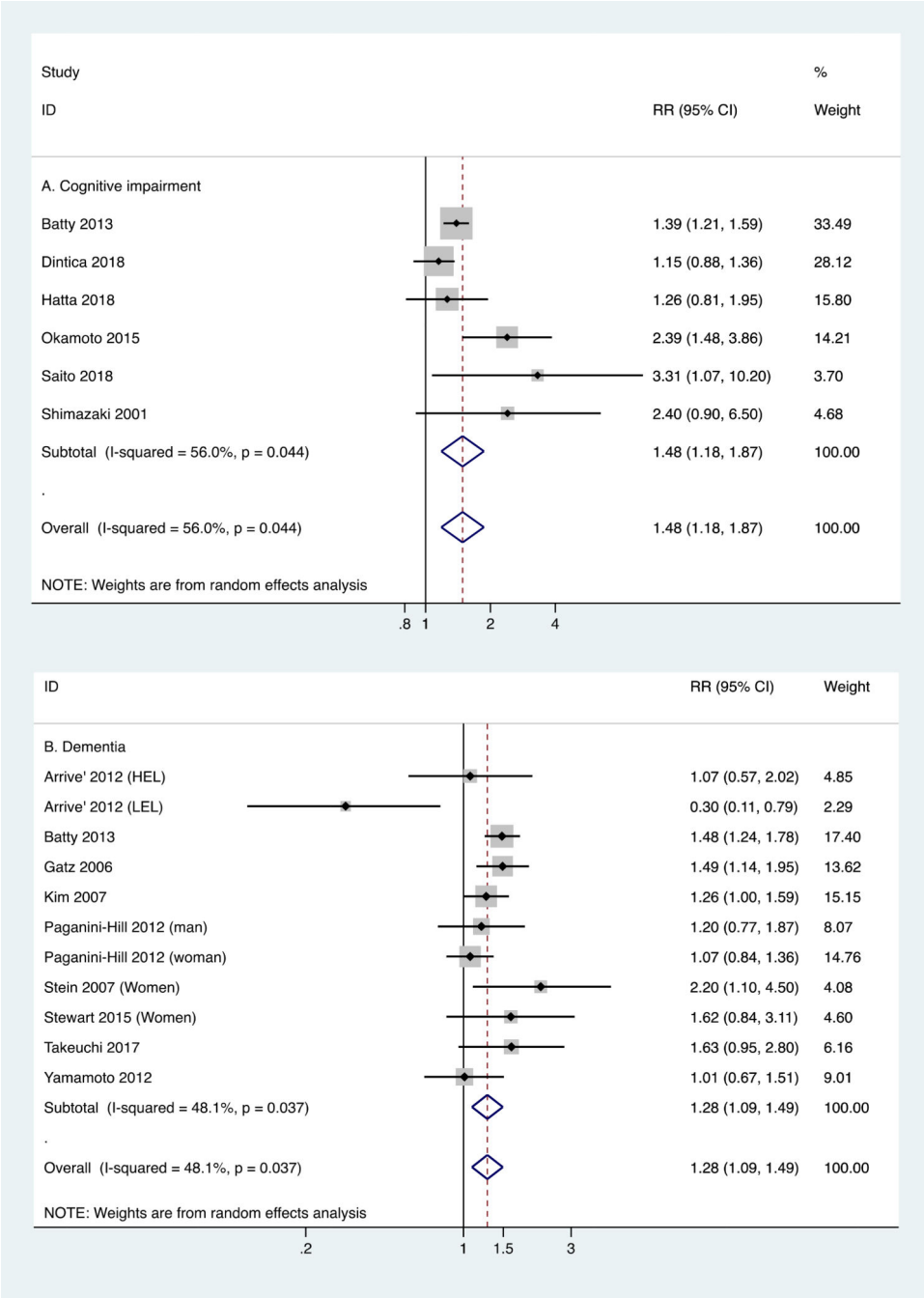

Figure 1.

Forest plot of tooth loss and risk of cognitive impairment (A) and dementia (B). Studies are pooled with a random-effects model; HEL, Higher education level, LEL, Lower education level

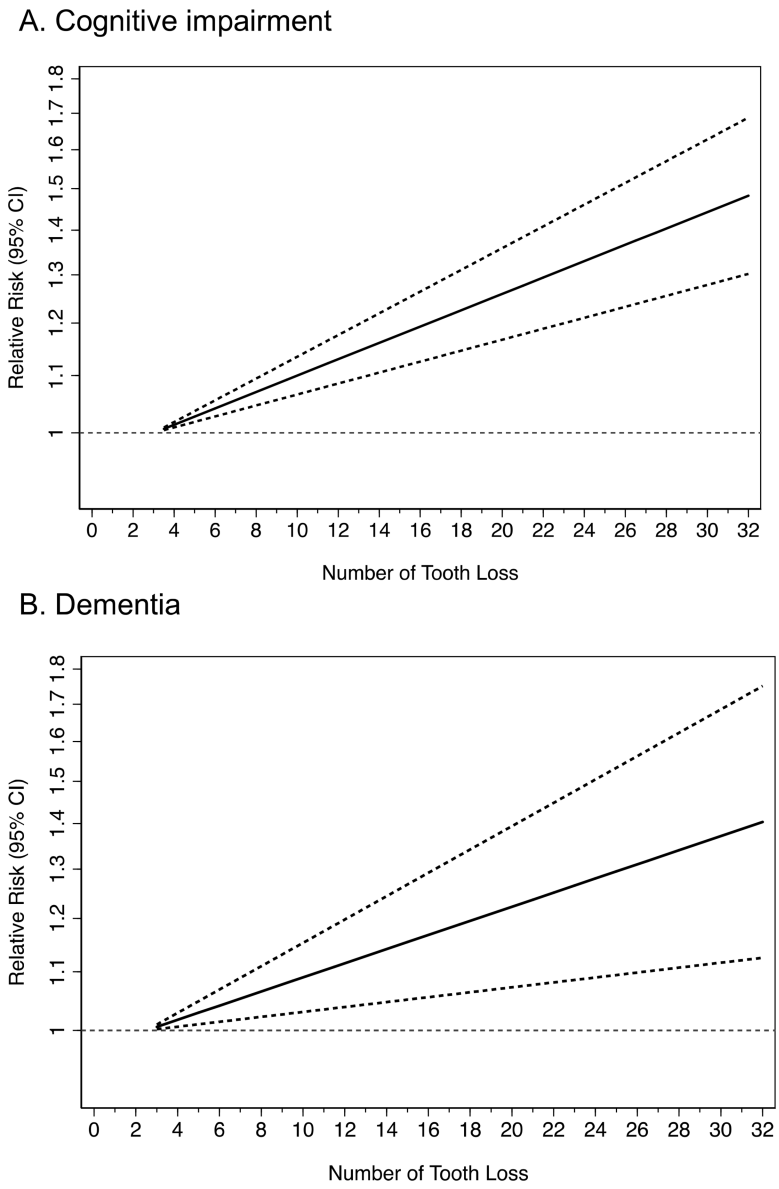

Figure 2.

Dose-response analysis of each one tooth loss increment and risk of cognitive impairment (A), dementia (B). The solid lines describe point estimates of the association between tooth loss and cognitive impairment or dementia risk; the dash lines represent 95% CIs

Table 1.

Subgroup analysis of the relative risk of cognitive impairment and dementia

Overall and subgroup analysis	No. of reports	RR (95%CI)	Effect model	I^2 (%)	*P* for heterogeneity
Total	17	1.34 (1.19–1.51)	Random	48.7%	0.01
Study design					
Prospective cohort	13	1.35 (1.13–1.62)	Random	58.9%	0.01
Retrospective cohort	4	1.20 (1.06–1.35)	Fixed	0.00%	0.35
Nested case-control	2	1.35 (1.14–1.61)	Fixed	33.7%	0.21
Study setting					
Community	16	1.33 (1.18–1.50)	Random	49.7%	0.01
Institution	1	2.40 (0.89–6.45)	/	/	/
Geographie region					
Europe	6	1.29 (1.08–1.54)	Random	62.1%	0.02
America	4	1.28 (1.10–1.47)	Fixed	33.7%	0.21
Asia	7	1.50 (1.16–1.95)	Random	49.8%	0.06
Sample size					
> 1000	9	1.34 (1.18–1.52)	Random	55.3%	0.03
≤ 1000	8	1.31 (1.10–1.55)	Random	48.2%	0.05
Follow-up period					
≥ 10 years	6	1.15 (1.02–1.28)	Random	57.8%	0.04
< 10 years	11	1.38 (1.27–1.49)	Fixed	35.4%	0.12
Denture status					
With denture	5	1.00 (0.90–1.11)	Fixed	0.0%	0.70
Without denture	5	1.55 (1.24–1.94)	Fixed	0.0%	0.47
Tooth loss assessment					
Clinical examination	10	1.49 (1.13–1.98)	Random	57.7%	0.01
Self-reported	7	1.31 (1.21–1.43)	Fixed	34.3%	0.17
NOS score quality					
High quality (score 7–9)	14	1.33 (1.12–1.58)	Random	54.6%	0.01
Intermediate quality (score 4–6)	3	1.41 (1.27–1.57)	Fixed	0%	0.75
Low quality (score 1–3)	0	/	/	/	/

Table 2.

Quality and strength of evidence for three outcomes

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)
	Risk with fewer tooth loss	Risk with more tooth loss			
Cognitive impairment Follow-up: mean 5.3 years	124 per 1,000	180 per 1,000 (159 to 201)	RR 1.48 (1.18 to 1.87)	17,310 (6 observational studies *)	⊕⊕⊕⊖ MODERATE
Dementia follow-up: mean 11.9 years	112 per 1,000	143 per 1,000 (121 to 165)	RR 1.28 (1.09 to 1.49)	27,904 (9 observational studies *)	⊕⊕⊕⊖ MODERATE

Note:

*Batty 2013's [27] study reported both the measurement of cognitive impairment and dementia.