Review

# Tooth Loss Increases the Risk of Diminished Cognitive Function: A Systematic Review and Meta-analysis

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**Abstract:** *Emerging evidence suggests that oral health is associated with cognitive function. This review aims to systematically assess this association in adult populations via prospective cohort study designs. Eligible study reports were identified by searching the MEDLINE (via Ovoid), EMBASE, PsycoINFO, and Cochrane Library databases. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated with a random effects model. From 1,251 identified articles, 10 were included in the systematic review and 8 in the meta-analysis. Random effects analysis showed, with statistically low heterogeneity, that individuals with suboptimal dentition (<20 teeth) were at a 20% higher risk for developing cognitive decline (HR = 1.26, 95% CI = 1.14 to 1.40) and dementia (HR = 1.22, 95% CI = 1.04 to 1.43) than those with optimal dentition (≥20 teeth). Studies on the association between periodontal disease and cognitive status showed conflicting results. Within the limits of the quality of published evidence, this meta-analysis lends further support to the hypothesis that tooth loss is associated with an increased risk of cognitive impairment and dementia.*

**Knowledge Transfer Statement:** *Based on the published literature, the results of this study show that the risk for cognitive impairment and dementia increases with loss of teeth. This information adds to the evidence showing links between oral and general health and suggests that oral health strategies aimed to preserve teeth may be important in reducing risk of systemic disease.*

**Keywords:** dementia, elderly, cohort study, dentition status, congnition disorders, oral health

## Introduction

The increase of cognitive impairment and its pathologic correlates, such as dementia and Alzheimer's disease, in aging populations is progressing worldwide and creating an important burden on health systems. About 25 million people suffer from dementia worldwide, with an incidence of 4.6 million per year (Prince et al. 2013). According to follow-up studies, annualized rates of conversion from mild cognitive impairment to dementia range from 4% to 25% (Aminoff and Daroff 2014).

Cognitively impaired individuals have signs and symptoms, such as loss of memory, attention, and executive functioning (Bozoki et al. 2001), and share common nonmodifiable risk factors, such as age, sex, and genetics (Beydoun et al. 2014). Cognitive impairment appears to be both irreversible and reversible, and research has focused on identifying factors that have the potential to decrease the risk of having cognitive decline (Beydoun et al. 2014).

Interestingly, in the last decade, researchers (Gatz et al. 2006; Hirano et al. 2008; Ono et al. 2010) have examined the impact of oral health—specifically, tooth loss and periodontal disease—on cognitive function.

Investigations using animal models have demonstrated that masticatory dysfunction caused by molar extraction, occlusal disharmony, or soft-diet feeding induces pathologic changes in the hippocampus and cerebral cortex, resulting in learning and memory deficits (Onozuka, Watanabe, et al. 2002; Watanabe et al. 2002; Ono et al. 2008). Surprisingly, these

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cognitive deficits were partially reversed when masticatory function was restored (Watanabe et al. 2002).

In humans, recent neuroimaging studies showed that brain regions linked to the memory and learning process are activated during chewing activities (Onozuka, Fujita, et al. 2002; Miyamoto et al. 2005; Narita et al. 2009). In fact, these studies revealed that masticatory activities increase cerebral blood flow and cognitive task performance (Hirano et al. 2008). Moreover, a few studies in edentate individuals indicate that oral rehabilitation of edentulism leads to an increase in regional blood volume, suggesting that mastication may be protective against brain degeneration and cognitive decline (Miyamoto et al. 2005; Narita et al. 2009). The association between poor oral health and cognitive impairment is also bilateral: patients with mild cognitive impairment, dementia, and Alzheimer's disease are more likely to have poorer oral hygiene, more periodontal disease, and tooth loss (Petersen and Yamamoto 2005). However, the oral health–cognitive decline association can be confounded by several common risk factors, such as aging, lifestyle, and systemic diseases such as diabetes (Machtei et al. 1999; Gatz et al. 2006; Cunningham and Hennessy 2015).

Better insight into the nature and extent of this association is therefore of great importance since it could lead to preventive interventions for cognitive performance. As such, the objective of this review was to systematically examine if poor oral health and its indicators (tooth loss and periodontal disease) lead to cognitive impairment and its most prevalent pathologic correlate (dementia). We focused on the following research question: Is there evidence from longitudinal studies to support the association between poor oral health (<20 teeth) and cognitive impairment in a human adult population?

## Material and Methods

### Protocol and Registration

This is a systematic review with an unpublished protocol. The PRISMA guidelines (preferred reporting items for systematic reviews and meta-analyses; Moher et al. 2009) were used for the report.

### Electronic Searches and Eligible Criteria

To identify the relevant studies, an electronic literature search was conducted for the period 1990 (date of established diagnostic criteria for cognitive decline and dementia; Jeste and Finkel 2000; Schmitt and Wichems 2006) to December 2014 **via** OVID in Embase, MEDLINE, PsycINFO, and the Cochrane Database of Systematic Reviews. That search was complemented by hand searching the list of references in the identified reviews (Table 1).

The search identified no randomized controlled trial, and to increase the level of evidence and allow the assessment of the temporal effect, prospective cohort studies were included. The target population included individuals aged ≥18 years with cognitive status/impairment as the outcome of interest. No language restriction was considered. Studies were excluded if the exposures did not include one of the oral health indicators (e.g., periodontal disease, number of teeth, use of denture). Studies with insufficient data or those that examined distinct mental health constructs, including anxiety,

**Table 1.**
Search Strategy Developed for MEDLINE via Ovid.

| Search | Queries |
|---|---|
| 1 | cognition disorders/ or mild cognitive impairment/ or exp dementia/ or Cognition/ or Cognitive Reserve/ |
| 2 | exp Memory/ |
| 3 | cogniti* or dementia* or alzheimer* or memory or memori* or overinclusion* amentia*).mp. |
| 4 | 1 or 2 or 3 |
| 5 | exp denture, complete/ or exp denture, partial/ |
| 6 | exp Oral Hygiene/ or exp Dental Care for Aged/ or exp Oral Health/ or exp bite force/ or exp dental occlusion/ |
| 7 | Periodontal Diseases/ or Tooth Loss/ or exp Periodontitis/ |
| 8 | (Parodontoses or Parodontosis or Periodontitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 9 | (masticat* or chew* or edent* or tooth loss or tooth losses or periodont*).mp. |
| 10 | (dental or Oral Health or oral hygiene or prosthetic rehabilitation or prosthetic treatment* or occlus* or denture* or bite-force).mp. |
| 11 | 5 or 6 or 7 or 8 or 9 or 10 |
| 12 | Cohort studies/ or exp Longitudinal studies/ |
| 13 | longitudinal or prospective or incidence study or incidence studies or incidence analysis or incidence analyses or cohort or concurrent study or concurrent studies or concurrent analysis or concurrent analyses or followup or follow-up).mp. |
| 14 | 12 or 13 |
| 15 | 4 and 11 and 14 |
| 16 | Humans/ |
| 17 | humans or human or woman or women or men or man or elderly or aged or senior citizen or senior citizens or seniors or adult or adults or people or peoples or patient or patients or individual or individuals).mp. |
| 18 | 16 or 17 |
| 19 | 15 and 18 |
| 20 | limit 19 to yr="1990 -Current" |

stress, or other outcomes of no interest to this review, were also excluded.

### Search Strategy

A detailed search strategy was developed for MEDLINE via Ovid interface (Table 1) and was revised for each of the other 3 databases (Appendix Tables 1–3). We created groupings of keywords and Medical Subject Headings that were internally combined with the Boolean term "OR." The first group consisted of terms related to cognitive impairment, dementia, and memory loss that were related to the outcomes of interest for this review. The second group represented the concept of oral health and included terms such as "tooth loss" and "periodontal disease." The third group consisted of the terms related to the study design. These 3 groups of terms were then combined using the Boolean term AND.

Two researchers (D.C.-K., R.F.S.) independently screened the title and abstract of each citation and identified eligible articles for full review. Disagreement between reviewers was discussed and resolved by consensus. All potential relevant studies were retained for full-text assessment (Fig. 1).

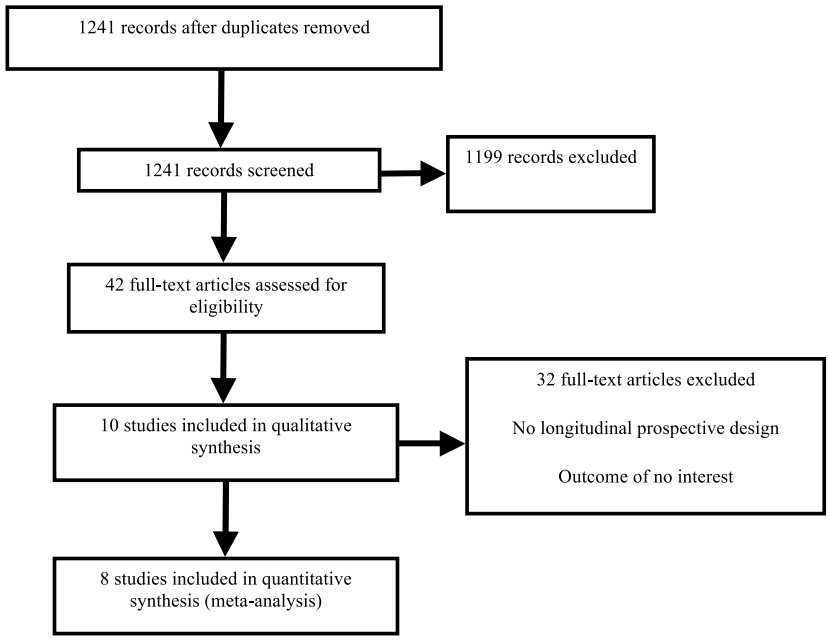
### Data Extraction

Data extraction was conducted independently by 2 reviewers (D.C.-K., M.A.) using a data extraction form. To avoid overlapping data, all publications related to the same study were verified, and the most recent report was selected for outcome assessment.

The information extracted from each article is shown in detail in Tables 2 and 3. In brief, these included authors, country, years of study, sample size, participant characteristics, dental and oral health status, type of measurement instrument, follow-up period, and main results, including the relative measures of association (odds ratio, hazard ratio [HR]) with 95% confidence intervals (95% CIs) from unadjusted and adjusted analyses.

When necessary, an email was sent to the authors of original papers to verify missing data or to ask for clarification of reported data (Stein et al. 2007; Kaye et al. 2010; Arrivé et al. 2012; Yamamoto et al. 2012; Reyes-Ortiz et al. 2013; Hansson et al. 2014).

**Figure 1.** Flowchart of publication assessment and selection for inclusion in the systematic review and for meta-analysis.




### Assessment of the Methodological Quality and Grading

Included studies were reviewed and assessed by 2 researchers (D.C.-K., M.A.) independently, according to the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology; von Elm et al. 2008). Studies were classified according to the 3 categories established by Olmos et al. (2008): A, the study is in agreement with >80% of the STROBE criteria; B, 50% to 80% of criteria fulfilled; C, <50% criteria achieved.

### Data Analysis

Meta-analyses were conducted to combine the results of the studies with similar exposures, similar outcome measures, and a minimum follow-up time of 12 mo. Optimal dentition was defined as having a minimum of 20 teeth (Sheiham et al. 2001; Armellini and von Fraunhofer 2004; Awad 2004; Kanno and Carlsson 2006; Morita et al. 2007). The relative measures of association (HRs and odds ratios, with 95% CIs) were standardized and pooled as a measure of association (Greenland and Longnecker 1992; de Craen et al. 2005). The pooled results were presented as HRs in the forest plot. Values <1 implied a risk-reducing effect of the exposure/disease at issue for all the relative measures of association, and values >1 implied a risk-increasing effect of the exposure/disease. The analyses were carried out with a random effects model that accounts for interstudy variation (Borenstein 2009).

The Cochran $Q$ test and $I^2$ statistic were used to test heterogeneity among studies. An $\alpha$ error of $P < 0.10$ and $I^2$ of at least 50% were taken as indicators of heterogeneity. Subgroup analyses were planned in the case of heterogeneity across studies.

All analyses were performed with Comprehensive Meta Analysis (version 2; Biostat, Englewood, NJ, USA).

## Results

### Study Selection

In total, 1,251 nonduplicate study reports were identified from database searches. Only 42 articles were eligible for full-text retrieval. Of these, 32 articles were excluded for the reasons presented in the flow diagram (Fig. 1).

**Table 2.**
Characteristics of the Included Studies and Summary of the Study Results on the Association of Dental Status and Cognitive Decline.

| Study[a]; Sample Size[b]; Age, y[c]; Follow-up, y | | | | |
|---|---|---|---|---|
| **Baseline Assessment of Dentition Status** | **Edentate, %** | **DV: Cognitive Decline Assessment** | **IVs** | **Results** |
| **Shimazaki et al. (2001), Japan; 517 (121/396); 79.7 ± 7.5; 6** | | | | |
| **Clinical examination: no. of teeth, use of denture** | 46.8 | Medical records, classification according to a 3-point Likert scale (good, fair, or poor) | Age, physical health, type of institution, and having cerebrovascular disorder | n = 156 developed cognitive decline; no significant association between cognitive decline and dental status |
| **Kaye et al. (2010), USA; 597 (597/0); 45.5 (28 to 70); 32** | | | | |
| **Clinical examination: no. of teeth, periodontal condition** | 5 | Neuropsychological testing: MMSE score, SCT | Age, education, smoking, diabetes, additional comorbidities, medication use, dietary intake | Each tooth lost per decade since the baseline dental examination increased the risks of low MMSE score (HR = 1.09; 95% CI = 1.01 to 1.18) and low spatial copying score (HR = 1.12; 95% CI = 1.05 to 1.18); risks greater per additional tooth with progression of alveolar bone loss (spatial copying: HR = 1.03; 95% CI = 1.01 to 1.06), probing pocket depth (MMSE: HR = 1.04; 95% CI = 1.01 to 1.09; spatial copying: HR = 1.04; 95% CI = 1.01 to 1.06) |
| **Batty et al. (2013), 20 countries; 11.140 (6.405/4.735); (55 to 88); 5** | | | | |
| **Self-report: no. of teeth, periodontal condition** | 21.1 | Neuropsychological testing: MMSE score | Age, sex, and several CV disease–related risk factors (including socioeconomic, psychological/ behavioral, and physiological factors) | *n* = 1,806 developed cognitive decline; edentate (HR = 1.39; 95% CI = 1.21 to 1.59) or those with fewer teeth (HR = 1.23; 95% CI = 1.10 to 1.38) had the higher risk of cognitive decline |
| **Reyes-Ortiz et al. (2013), HISPANIC EPESE, USA; 1.967 (795/1 172); ≥65; 5** | | | | |
| **Self-administered questionnaire: no. of teeth** | 43.6 | Neuropsychological testing: MMSE score, global domains | Age, sex, education, language, last dental visit, near vision impairment, hypertension, diabetes, heart attack, stroke, depressive symptoms, and ADL | The longitudinal analyses of 5-y data showed that those with fewer teeth vs. those with more teeth had a greater decline in total MMSE scores; there was a yearly decrease of 0.12 points in adjusted models (SE ± 0.05, $P < 0.01$) |
| **Naorungroj (2014), USA; 911 (352/559); 64.7 ± 4.3; 8** | | | | |
| **Clinical examination: no. of teeth, periodontal condition** | 13.8 | Neuropsychological testing: DWR, DSS, WF | Age, sex, education, apolipoprotein ε4 allele, race, income, CV risk factors, stroke and coronary heart disease | No significant association between cognitive decline and dental status |

95% CI, 95% confidence interval; ADL, activities of daily living; CV, cardiovascular; DSS, digit symbol substitution; DV, dependent variable; DWR, delayed word recall; HR, hazard ratio; IV, independent variable; MMSE, Mini Mental State Examination; SCT, spatial copying task; WF, word fluency.
[a]Author (year), survey, country.
[b]Sample size at last follow-up (male/female).
[c]Age: mean ± SD, median (min to max).

**Table 3.**
Characteristics of the Included Studies and Summary of the Study Results on the Association of Dental Status and Dementia.

| Study[a]; Sample Size[b]; Age, y[c]; Follow-up, y | | | | |
|---|---|---|---|---|
| **Baseline Assessment of Dentition Status** | **Edentate, %** | **DV: Dementia Assessment** | **IVs** | **Results** |
| **Stein et al. (2007), Nun Study, USA; 101 (0/101); 84 (75 to 98); 10** | | | | |
| Dental/medical records: no. of teeth, use of dentures, periodontal condition | NA | Neuropsychological testing: MMSE score; ADL, DWR, DSS, WF | Age, education, and apolipoprotein ε4 allele | n = 32 developed dementia; those with fewer teeth had the higher risk of developing dementia (HR = 2.20; 95% CI = 1.1 to 4.5). |
| **Arrivé et al. (2012), PAQUID, France; 405 (184/221); 70 (66 to 80); 15** | | | | |
| Clinical examination: no. of teeth, periodontal condition | NA | Neuropsychological testing: DSM-III-R | Sex, BMI, alcohol intake, diabetes, depressive symptoms, hypertension, and history of vascular disease | n = 72 developed dementia; those with lower education and fewer teeth had statically significant lower risk of dementia (HR = 0.30; 95% CI = 0.11 to 0.79)—however, when adjusted for education (combined high and low categories), the association became nonsignificant |
| **Paganini-Hill et al. (2012), Leisure World Cohort, USA; 5,468 (1,733/3,735); 81 (52 to 105); 18** | | | | |
| Self-administered questionnaire: no. of teeth, use of dentures | 11 | Neuropsychological testing: MMSE score, medical records | Age, education, smoking, BMI, alcohol/caffeine intake, medication use, diabetes, high blood pressure, angina pectoris, heart attack, stroke, rheumatoid arthritis, cancer, head trauma, and family history of dementia | *n* = 1,145 developed dementia; men with fewer teeth and those without dentures had higher risk of dementia (HR = 1.91; 95% CI = 1.13 to 3.21); this association not statistically significant in women |
| **Yamamoto et al. (2012), AGES, Japan; 4,425 (2,159/2,266); 72.7 ± 5.9; 4** | | | | |
| Self-administered questionnaire: no. of teeth, use of dentures | 53.2 | Validated multidimensional dementia assessment questionnaire (developed by Ministry of Health, Labor and Welfare in Japan) | Age, household income, BMI, presence of illness, alcohol intake, exercise, and forgetfulness | n = 220 developed dementia; those with the fewest teeth without dentures had the highest risk of dementia (HR = 1.85; 95% CI = 1.04 to 3.31) |
| **Batty et al. (2013), ADVANCE, 20 countries; 11,140 (6,405/4,735); 55 to 88; 5** | | | | |
| Self-administered questionnaire: no. of teeth | 21.1 | Neuropsychological testing: MMSE score, DSM-IV | Age, sex, and several cardiovascular disease–related risk factors | *n* = 109 developed dementia; edentate (HR = 1.48; 95% CI = 1.24 to 1.78) or those with fewer teeth (HR = 1.24 95% CI = 1.05 to 1.46) had the higher risk of dementia |
| **Hansson et al. (2014), Betula, Sweden; 2,075 (917/1,158); 71.2 ± 8.2; 20** | | | | |
| Self-administered questionnaire: no. of teeth, use of dentures | 25.3 | Neuropsychological testing: DSM-IV | Age, sex, education, and apolipoprotein ε4 allele | *n* = 403 developed dementia; no significant association between dementia and dental status |

95% CI, 95% confidence interval; ADL, activities of daily living; BMI, body mass index; DSM-III R, *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; DSS, digit symbol substitution; DV, dependent variable; DWR, delayed word recall; HR, hazard ratio; IV, independent variable; MMSE, Mini Mental State Examination; NA, not available, WF, word fluency.
[a]Author (year), survey, country.
[b]Sample size at last follow-up (male/female).
[c]Age: mean ± SD, median (min to max).

### Characteristics of Studies

The detailed characteristics of the 10 studies included in the review are shown in Tables 2 and 3. Apart from Shimazaki et al. (2001), all other studies on the relationship between tooth loss/periodontal disease and cognitive status were secondary data analyses and ad hoc in nature, with samples ranging from 101 (Stein et al. 2007) to 11,140 individuals (Batty et al. 2013). Data were obtained from cohort or surveillance studies conducted in the United States (Stein et al. 2007; Kaye et al. 2010; Paganini-Hill et al. 2012; Reyes-Ortiz et al. 2013; Naorungroj 2014), Sweden (Hansson et al. 2014), France (Arrivé et al. 2012), and Japan (Shimazaki et al. 2001; Yamamoto et al. 2012). The latest publication was from 2014 (Hansson et al. 2014; Naorungroj 2014) and the earliest from 2001 (Shimazaki et al. 2001).

### Study Outcomes, Indicators of Oral Health, and Measurements

In 4 studies, the reported outcome was cognitive decline (Shimazaki et al. 2001; Kaye et al. 2010; Reyes-Ortiz et al. 2013; Naorungroj 2014); in 5, the outcome was dementia (Stein et al. 2007; Arrivé et al. 2012; Paganini-Hill et al. 2012; Yamamoto et al. 2012; Hansson et al. 2014); and 1 study reported both these outcomes (Batty et al. 2013). Tooth loss was the primary oral health indicator in all studies. Only half the included studies assessed and reported on periodontal disease (Stein et al. 2007; Kaye et al. 2010; Arrivé et al. 2012; Batty et al. 2013; Naorungroj 2014).

Cognitive function was ascertained during follow-ups ranging from 4 y (Yamamoto et al. 2012) to 32 y (Kaye et al. 2010). Four studies measured and reported cognitive status at baseline and at the last follow-up (Shimazaki et al. 2001; Paganini-Hill et al. 2012; Yamamoto et al. 2012; Hansson et al. 2014). One study reported the cognitive status at each annual follow-up (Stein et al. 2007), and the other 5 studies assessed this outcome every 2 y (Arrivé et al. 2012; Batty et al. 2013; Reyes-Ortiz et al. 2013), 3 y (Kaye et al. 2010), or 4 y (Naorungroj 2014).

**Table 4.**
Classification of Studies according to the STROBE Statement.

| Study | Fulfilled STROBE Criteria, % | Level of Quality[a] |
|---|---|---|
| Shimazaki et al. (2001) | 68.2 | B |
| Stein et al. (2007) | 77.3 | B |
| Kaye et al. (2010) | 77.3 | B |
| Arrivé et al. (2012) | 90.9 | A |
| Paganini-Hill et al. (2012) | 81.8 | A |
| Yamamoto et al. (2012) | 86.4 | A |
| Batty et al. (2013) | 72.7 | B |
| Reyes-Ortiz et al. (2013) | 59.1 | B |
| Hansson et al. (2014) | 50.0 | B |
| Naorungroj (2014) | 77.3 | B |

STROBE statement: von Elm et al. (2008).
[a]A, the study is in agreement with >80% of the STROBE criteria; B, 50% to 80% criteria fulfilled; C, <50% criteria achieved.

The assessment of cognitive function and diagnosis of cognitive impairment or dementia was based on the patient's medical record (Shimazaki et al. 2001; Paganini-Hill et al. 2012; Yamamoto et al. 2012) or via clinical or standard neuropsychological examination by a neurologist, psychiatrist, or other health professional (Stein et al. 2007; Kaye et al. 2010; Arrivé et al. 2012; Batty et al. 2013; Reyes-Ortiz et al. 2013; Hansson et al. 2014; Naorungroj 2014). Genetic predisposition to dementia (Stein et al. 2007; Hansson et al. 2014; Naorungroj 2014), as well as depressive symptoms (Arrivé et al. 2012; Batty et al. 2013; Reyes-Ortiz et al. 2013), was assessed in 3 studies.

Tooth loss and periodontal disease were assessed by clinical examination/full-mouth radiographs in 4 studies (Shimazaki et al. 2001; Stein et al. 2007; Kaye et al. 2010; Arrivé et al. 2012) and by self-administrated questionnaires in the 6 other included studies (Paganini-Hill et al. 2012; Yamamoto et al. 2012; Batty et al. 2013; Reyes-Ortiz et al. 2013; Hansson et al. 2014; Naorungroj 2014).

### Quality of the Reports

The 2 reviewers were in complete agreement regarding the quality of studies reports. According to the Olmos classification (von Elm et al. 2008), 3 studies had a high-grade quality (A), fulfilling >80% of the STROBE criteria. Seven studies had a moderate level of quality (B), thus achieving 50% to 80% of STROBE criteria (Table 4).

All studies reported the sample size of the original cohort, as well as the sample size used for the actual data analysis. However, none of the studies provided a sample size estimation or power calculation based on the study objective. Two studies reported on loss to follow-up (Arrivé et al. 2012; Paganini-Hill et al. 2012), and only 1 study gave details on missing data (Yamamoto et al. 2012). Most studies reported on subgroup and sensitivity analyses (Shimazaki et al. 2001; Stein et al. 2007; Kaye et al. 2010; Arrivé et al. 2012; Paganini-Hill et al. 2012; Yamamoto et al. 2012; Batty et al. 2013; Hansson et al. 2014; Naorungroj 2014). To reduce the risk of bias, all studies considered a number of confounders in their statistical analyses. All studies, except 1, provided information on the source of funding (Reyes-Ortiz et al. 2013).

### Periodontal Disease, Cognitive Impairment, and Dementia

The 5 studies that examined the relation between periodontal disease and cognitive impairment or dementia (Stein et al. 2007; Kaye et al. 2010; Arrivé et al. 2012; Batty et al. 2013; Naorungroj 2014) showed conflicting results.

Kaye et al. (2010) followed 597 men over a period of 32 y and showed that progression of alveolar bone loss or pocket depth could increase the risk of cognitive decline by 2% to 5%. According to this study, periodontal disease progression predicted cognitive decline (for spatial copying task: HR = 1.03, 95% CI = 1.01 to 1.06; for MMSE score: HR = 1.04, 95% CI = 1.01 to 1.09). However, this association was not seen in the other 4 studies (Stein et al. 2007; Arrivé et al. 2012; Batty et al. 2013; Naorungroj 2014).

### Tooth Loss, Cognitive Impairment, and Dementia

As presented in Tables 2 and 3, according to the majority of studies (Stein et al. 2007; Kaye et al. 2010; Paganini-Hill et al. 2012; Yamamoto et al. 2012; Batty et al. 2013; Reyes-Ortiz et al. 2013), tooth loss was a predictor of cognitive impairment and dementia even after adjusting for several confounders. However, the studies by Shimazaki et al. (2001), Hansson et al. (2014), and Naorungroj (2014) did not show this association.

In the study by Arrivé et al. (2012), a significant interaction ($P = 0.002$) was found between education level and number of missing teeth. The HR for dementia was 1.27 (95% CI = 0.70 to 2.31; $P = 0.429$) in persons with >10 missing teeth and with higher levels of education and 0.40 (95% CI = 0.17 to 0.94; $P = 0.03$) in those edentate with lower levels of education.

Since number of teeth lost was the only variable that was measured in all studies, a meta-analysis was conducted to pool the study results based on this indicator of oral health. As dementia was reported as a distinct outcome in 6 articles, 2 separate analyses were conducted.

The pooled results showed that individuals with <20 teeth (suboptimal dentition) compared with those with optimal dentition (≥20 teeth) were at higher risk for cognitive impairment (HR = 1.26, 95% CI = 1.14 to 1.40; $Z = 4.72$; $P < 0.0001$; $I^2 = 0\%$, $P = 0.419$; Fig. 2A) and dementia (HR = 1.22, 95% CI = 1.04 to 1.43; $Z = 2.48$; $P = 0.013$; $I^2 = 33\%$, $P = 0.185$; Fig. 2B).

## Discussion

To our knowledge, this is the first systematic review and meta-analysis to investigate the effect of poor oral health and, specifically, tooth loss and periodontal disease on cognitive status. The results indicate that individuals with suboptimal dentition (<20 teeth) have a 26% increased risk of cognitive decline and a 22% increased risk of dementia. Furthermore, the results showed low effects of heterogeneity.

These results are broadly in support of previous human and animal study findings on this topic and strengthen the hypothesis that tooth loss is likely to increase the risk of systemic disease (Watanabe et al. 2002; Wang et al. 2013; Liljestrand et al. 2015). Our findings showed that only 1 of the 6 studies on the association between tooth loss and dementia (Arrivé et al. 2012) had contrasting results. In that study, tooth loss was associated with a lower risk of dementia but only in people with low education levels. The authors of the study related this unexpected finding to the suppression of inflammation by tooth extraction. We appreciate the response of the authors to our suggestion to send us the results of an adjusted model, considering education as an independent variable. This supplemental data analysis showed that education acts as a confounding factor for this association.

In the present meta-analysis, presence of at least 20 teeth was used to define optimal dentition based on the literature review (Sheiham et al. 2001; Shimazaki et al. 2001; Kanno and Carlsson 2006). According to this analysis, it could be inferred that individuals with suboptimal dentition may experience cognitive impairment later in life.

Previous research suggests 3 plausible mechanisms that may account for the association between tooth loss and cognitive impairment. First, tooth loss may lead to cognitive decline via reducing the mastication-induced sensory stimulation to the brain (Onozuka, Fujita, et al. 2002; Onozuka, Watanabe, et al. 2002; Rothman and Greenland 2005; Hirano et al. 2013).

Second, dentition status can be linked to cognitive impairment via the nutritional pathway (Paganini-Hill et al. 2012; Yamamoto et al. 2012). In fact, suboptimal dentition and inadequate masticatory performance have been shown to be associated with poor nutritional intake (Krall et al. 1998). The association between nutrition and cognitive status is well documented (Tucker et al. 2005). However, the findings of this review did not allow for an explanation of the role of nutrition in the oral health–cognitive status association. This could be explained by the use of a nonsensitive instrument for nutritional assessment. In fact, in the studies included in this review (Kaye et al. 2010; Arrivé et al. 2012; Paganini-Hill et al. 2012; Yamamoto et al. 2012; Batty et al. 2013), body mass index (BMI) was used as a proxy for nutritional assessment. While BMI is suggested as a tool for nutritional screening, it cannot replace comprehensive nutritional evaluation (Mascie-Taylor and Goto 2007; Bahat et al. 2012).

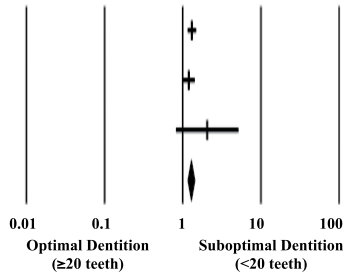
Finally, it has been hypothesized that the presence of periodontal disease may play a role in cognitive diseases (Yaffe et al. 2004). This review showed conflicting results on that potential mechanism. From a total of 5 studies (Stein et al. 2007; Arrivé et al. 2012; Batty et al. 2013; Naorungroj 2014), in only 1 study was a statistically significant association found between periodontal condition and cognitive status (Kaye et al. 2010). However, the wide variability in periodontal measurement methods used in the included studies hampers data interpretation in this regard. Furthermore, the majority of the reviewed studies did not include data on inflammatory biomarkers. Such data could be used to provide evidence on the role of periodontal disease in cognitive impairment and thus facilitate interpretation of the findings (Yaffe et al. 2004).

A strength of the present review is its focus on cohort research design. A prospective cohort is the suitable research design for etiologic studies that allow the testing of temporal effects and

**Figure 2.** Forest plot showing the association of dentition status (**A**) with the risk of cognitive impairment and (**B**) with the risk of dementia.

**(A)**

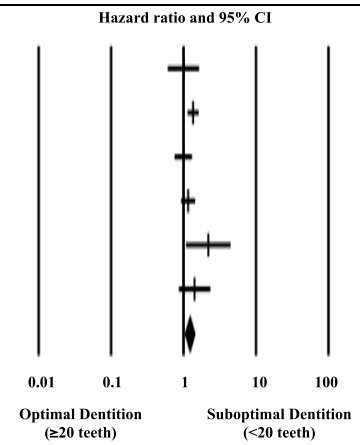
| Study | Relative Weight | Hazard ratio | Lower Limit | Upper Limit | Z-value | P-value |
|---|---|---|---|---|---|---|
| Batty et al., 2013 | 64.30 | 1.31 | 1.15 | 1.48 | 4.19 | 0.000 |
| Ortiz-Réyes et al., 2013 | 34.50 | 1.17 | 0.98 | 1.38 | 1.75 | 0.081 |
| Shimazaki et al., 2001 | 1.20 | 1.80 | 0.72 | 4.51 | 1. 26 | 0.209 |
| Overall | | 1.26 | 1.14 | 1.40 | 4.52 | <0.001 |




**Heterogeneity:** $Tau^2 = 0.000$, Q = 7.52, df = 2, $p = 0.42$, $I^2 = 0.000$

**(B)**

| Study | Relative Weight | Hazard ratio | Lower Limit | Upper Limit | Z-value | P-value |
|---|---|---|---|---|---|---|
| Arrivé et al., 2012 | 8.51 | 0.99 | 0.61 | 1.63 | -0.02 | 0.987 |
| Batty et al., 2013 | 32.42 | 1.36 | 1.14 | 1.61 | 3.44 | 0.001 |
| Hansson et al., 2014 | 20.25 | 0.99 | 0.75 | 1.30 | -0.07 | 0.943 |
| Paganini-Hill et al., 2012 | 25.94 | 1.16 | 0.93 | 1.44 | 1.30 | 0.195 |
| Stein et al., 2007 | 4.55 | 2.20 | 1.09 | 4.45 | 2.19 | 0.028 |
| Yamamoto et al, 2012 | 8.34 | 1.42 | 0.86 | 2.34 | 1.38 | 0.169 |
| Overall | | 1.22 | 1.04 | 1.43 | 2.49 | 0.013 |




**Heterogeneity:** $Tau^2 = 0.012$, Q = 7.52, df = 5, $p = 0.185$, $I^2 = 33.49$

the discovery of mechanisms by reducing the risk of recall bias and measurement error. Nonetheless, this meta-analysis has some limitations. First, there was considerable variation in outcome measures and how these were reported in a number of areas: type and version of the neurocognitive testing tool, period of the follow-up, data-reporting method, and severity of cognitive decline and dementia. Given these issues, we used a random effects model to account for this variability (Higgins and Green 2011). Second, we should be cautious when interpreting these data, considering risk of bias and methodological quality of the studies included in this review (von Elm et al. 2008). For instance, the majority of the included studies did not explain how missing data were addressed or did not provide sample size or power calculations. Finally, the small number of included studies did not allow us to test for publication bias.

The results of our systematic review highlight the need for interdisciplinary research and the production of high-quality data in this research domain. Furthermore, the use of neuroimaging techniques may help to better explain the underlying mechanism of the association of oral health with cognitive function. This will allow further implementation of oral health population-based strategies to prevent the development of systemic diseases.

In conclusion, this systematic review offers evidence that tooth loss increases the risk of cognitive impairment and dementia. There is a need for further research to identify the biological basis for this association.

## Author Contributions

D. Cerutti-Kopplin, E. Emami, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; R.F. de Souza, J. Feine, D.M. Padilha, L. Booij, contributed to data interpretation, critically revised the manuscript; M. Ahmadi, contributed to data interpretation, drafted the manuscript; P. Rompré, contributed to data analysis, drafted the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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