Tooth loss as a risk factor for dementia: systematic review and meta-analysis of 21 observational studies

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Abstract

Background: Tooth loss is suggested to be associated with an increased risk of dementia in many studies. But the relationship between tooth loss and dementia is not yet fully understood. This systematic review and meta-analysis aimed to determine the relative effect of tooth loss on dementia risk.

Methods: An electronic search of PubMed, Scopus, Embase, and Web of Knowledge was conducted in March 2018 to identify relevant observational studies with the English language restriction. Studies were included if they assessed the relationship between tooth loss and risk of dementia. Study quality was detected by the modified Downs and Black scale. Odds risks (ORs) were pooled using a random-effects model in the crude model.

Results: The literature search initially yielded 1574 articles, and 21 observational studies published between 1994 and 2017 were finally included for the analyses. The crude results with random-effects model showed that patients with multiple tooth loss had higher incidence of dementia (OR 2.62, 95% CI 1.90–3.61, P < 0.001, I² = 90.40%). The association remained noted when only adjusted results were pooled from 18 studies (OR 1.55, 95% CI 1.41–1.70, P = 0.13, I² = 28.00%). Meta-regression analysis showed that study design explained about 16.52% of heterogeneity in the crude model. The overall quality rating scores of studies ranged from 11 to 16.

Conclusions: Findings from this review evidenced that tooth loss is positively associated with an increased risk of dementia in adults. Future well-designed longitudinal researches examining the direct and indirect relationship between tooth loss and dementia risk are encouraged.

Keywords: Dementia, Cognitive impairment, Tooth loss, Risk assessment, Meta-analysis

Background

Dementia is characterized by cognitive and functional decline and neuropsychiatric symptoms caused by irreversible neurodegenerative diseases. The global population is aging at a rapid pace due to rising life expectancy and over 47 million people live with dementia in 2016. The prevalence of dementia results in negative impacts on people’s life quality and economy according to the 2016 World Alzheimer Report [1]. To our knowledge, there is no effective anti-dementia drug available for the management of dementia. Therefore, it is in great need to identify modifiable risk factors for preventing cognitive impairment.

Tooth loss is prevalent in patients with dementia and it is a worldwide public health issue in older adults [2], impacting negatively on their quality of daily life, such as chewing, swallowing, and social life [3–5]. Evidence has shown that tooth loss is not only associated with oral health, but also with systemic health [6]. Recently, increasing studies have focused on the link between tooth loss and the risk of dementia [7–12]. There are several potential mechanisms by which tooth loss can negatively impact cognitive function. Periodontitis is one of the main causes of tooth...
loss, which is able to increased levels of pro-inflammatory mediators such as IL-1, IL-6 and TNF-α in the plasma, contributing to the aggravation of neuroinflammatory processes in brain and eventually resulting in cognitive decline [13–15]. Besides, masticatory disorder due to tooth loss can lead to poor nutrition, and reduce cerebral blood flow, which may be linked to memory deficits [9, 10]. It has been supported by several animal studies that tooth loss may induce decreased acetylcholine levels due to masticatory dysfunction, and lead to reductions in the number of pyramidal cells in the hippocampus, provoking cognitive dysfunction [16, 17].

A growing number of primary studies have demonstrated a close relationship between tooth loss and incidence of dementia, suggesting that tooth loss may be a modifiable risk factor for dementia [18–27]. However, this association is not noted in some studies [28–38]. To our knowledge, there are only two limited meta-analysis released by Shen et al [39] and Oh et al [40], exploring the relationship between tooth loss and cognitive impairment. In fact, some vital studies were not included without clear reasons, although Shen and colleagues have included observational studies from different study designs in the review. Moreover, the flow diagram of identification and selection process of studies could not be found in the analysis [39, 40]. Additionally, qualitative evaluation of selected studies and confounders for adjusted results of included studies were not demonstrated in the paper. As for the meta-analysis by Oh and colleagues, they intended to include cohort studies to prevent significant selection bias from cross-sectional studies [40]. However, one of the included studies is a cross-sectional design study, which was released by Luo et al [18]. Based on that, we therefore conducted a well-designed systematic review and meta-analysis of observational studies describing the association between tooth loss and the incidence of dementia in adults. We hope that our results can shed some light on the prevention of dementia in the future.

![Flow diagram of identification and selection process of studies](image-url)
| Author /Year  | Country | Sample size | Study design | Age, yr | Main exposure definition | Exposure cut-off point | Accessment of cognitive function | Effect size and crude association results with 95%CI highest vs. lowest category | Effect size and adjusted association results with 95%CI highest vs. lowest category | Adjustment | Quality scores |
|--------------|---------|-------------|--------------|---------|---------------------------|------------------------|------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|----------------|----------------|
| Luo et al (2015) [18] | China | 3063 | Cross sectional | ≥60 | Number of teeth missing | 0–3, 4–6, 7–16, >16 | DSM-IV | 3.65 (2.75–4.86) | 1.56 (1.12–2.18) | Sex, age, education year, living alone, overweight, cigarette smoking, alcohol drinking, anxiety, depression, heart disease, hypertension, diabetes, and Apolipoprotein E-ε | 15 |
| Peres et al (2014) [19] | Brazil | 1705 | Cross sectional | ≥60 | Number of teeth present | ≥10, <10, 0 | MMSE | 640 (3.40–12.10) | 3.30 (1.20–9.30) | Sex, age, race, income, education, smoking, depression, diabetes, cardio-vascular disease, and hypertension | 14 |
| Nilsson et al (2014) [20] | Sweden | 1147 | Cross sectional | 60–96 | Number of teeth present | ≥20, 1–19, 0 | MMSE | 920 (5.90–14.30) | 3.20 (1.90–53.00) | Age and education | 15 |
| Wang et al (2014) [28] | China | 930 | Cross sectional | ≥65 | Number of teeth present | ≥20, <20 | MMSE | 1.54 (1.13–2.10) | 1.30 (0.93–1.81) | Age, gender and life style habits | 14 |
| Park et al (2013) [21] | Korea | 438 | Cross sectional | ≥50 | Number of teeth missing | 0–5, 6–10, >10 | MMSE | 2.69 (1.57–4.64) | 2.25 (1.26–4.02) | Age, gender, education, hypertension, diabetes, hyperlipidemia and current smoking | 13 |
| Saito et al (2013) [22] | Japan | 462 | Cross sectional | ≥60 | Number of teeth present | 22–32, 11–21, 0–10 | MMSE | 2733 (3.62–206.21) | 20.21 (2.20–185.47) | Age, gender, education, smoking, alcohol intake, positive history of diseases, TMIG-IC score, and CES-D total score | 13 |
| Lexomboon et al (2012) [29] | Sweden | 557 | Cross sectional | ≥77 | Number of teeth missing | Multiple tooth loss | MMSE | 2.10 (1.35–3.25) | 1.36 (0.84–2.19) | Sex, age, and education | 12 |
| Okamoto et al (2010) [23] | Japan | 4061 | Cross sectional | ≥65 | Number of teeth present | 22–32, 11–21, 0–10 | MMSE | – | 2.18 (1.51–3.14) | Depressive symptoms, age, sex, length of education, frequency of drinking, smoking habit, time spent walking every day, positive history of cancer and diabetes mellitus, and the levels of serum albumin, total cholesterol, and low-density lipoprotein cholesterol | 12 |
| Stewart et al (2007) [24] | England | 4032 | Cross sectional | ≥65 | Number of teeth present | >0, 0 | AMTS | 3.59 (2.36–5.47) | 2.61 (1.49–4.28) | Age, sex, education, sampling area, disability, and BMI | 12 |

Note: CI Confidence interval, AMTS Abbreviated Mental Test Score, TMIG-IC The Tokyo Metropolitan Institute of Gerontology Index of Competence, CES-D The Center for Epidemiologic studies depression scale, BMI Body mass index, MMSE Mini-mental status examination, DSM-IV The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
| Author / Year                      | Country   | Sample size | Study design | Age, yr | Main exposure definition | Exposure cut-off point | Accessment of cognitive function | Effect size and crude association results with 95% CI highest vs. lowest category | Effect size and adjusted association results with 95% CI highest vs. lowest category | Adjustment                                                                 | Follow-up, yr | Quality scores |
|-----------------------------------|-----------|-------------|--------------|---------|--------------------------|-----------------------|-------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------|----------------|
| Takeuchi et al (2017) [30]        | Japan     | 1566        | Cohort       | ≥60     | Number of teeth present  | ≥20, 10–19, 1–9, 0    | DSM-III R                    | 3.83 (2.47–5.93) 1.63 (0.95–2.80)                                                                 | Sex, age, occupation, education, hypertension, diabetes mellitus, history of stroke, alcohol intake, tooth brushing frequency, regular visits to the dentist, and denture use. | 51 6           | 16            |
| Stewart et al (2015) [31]         | Sweden    | 697         | Cohort       | 70–92   | Number of teeth present  | ≥25, 21–24, 9–20, 0–8 | DSM-III R                    | –                                                                             | 1.62 (0.84–3.11)                                                                 | Age, education, social class, and vascular risk factors                                                                 | 37 13          |                |
| Batty et al (2013) [30]           | 20 Countries | 11,140   | Cohort       | 55–88   | Number of teeth present  | ≥22, 1–21, 0          | MMSE                          | –                                                                             | 1.48 (1.24–1.78)                                                                 | Age, sex, socio-economic CVD risk factors, treatment allocation and ethnicity                                                                 | 5 14            |                |
| Yamamoto et al (2012) [32]        | Japan     | 4425        | Cohort       | ≥65     | Number of teeth present  | ≥20, 519, 0           | Standardized questionnaire    | 3.42 (1.05–11.08) 1.41 (0.42–4.70)                                                                 | Age, adjusted household income, BMI, present illness, alcohol consumption, exercise, and forgetfulness | 4 15            |                |
| Paganini-Hill et al (2012) [33]   | USA       | 5468        | Cohort       | 52–105  | Number of teeth present  | 26–32, 16–25, 1–15, 0 | MMSE                          | 0.84 (0.67–1.06) –                                                                 | –                                                                             | –                                                                                                                       | 18 13          |                |
| Arrivé et al (2011) [34]          | France    | 405         | Cohort       | 66–80   | Number of teeth missing  | < 11 ≥11              | DSM-III R                    | 1.35 (0.81–2.25) –                                                                 | –                                                                             | Age, gender and education, reported diet, vascular disease/risk, BMI and MAC, albumin and cholesterol | 15 12          |                |
| Kim et al. (2007) [35]            | Korea     | 686         | Cohort       | ≥65     | Number of teeth present  | ≥28, 25–27, 15–24, 1–14, 0 | DSM-IV                        | 1.38 (1.12–1.69) 1.26 (1.00–1.59)                                                                 | –                                                                             | –                                                                                                                       | 18 13          |                |
| Stein et al (2007) [26]           | USA       | 101         | Cohort       | 75–98   | Number of teeth present  | 10–28, 0–9             | MMSE                          | 2.69 (1.07–6.73) 2.20 (1.10–4.50)                                                                 | Age, education, and apolipoprotein E4 allele                                                                 | 12 13          |                |
| Shimazaki et al (2001) [36]       | Japan     | 517         | Cohort study | ≥65     | Number of teeth present  | >20, 1–19, 0           | Historical diagnosis information from medical records | 5.20 (2.00–13.10) 2.40 (0.90–6.50)                                                                 | Age, and classification of institution, physical health status, and cerebrovascular disorder | 6 13            |                |

Notes: BMI Body mass index, CI Confidence interval, CVD Cardiovascular disease, DSM-IV The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, DSM-III R Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised, MAC Mid arm circumference, MMSE The Mini-Mental State Examination
| Author / Year          | Country | Sample size | Study design | Age, yr | Main exposure definition | Exposure cut-off point | Assessment of cognitive function | Effect size and crude association results with 95%CI highest vs. lowest category | Effect size and adjusted association results with 95%CI highest vs. lowest category | Adjustment | Quality scores |
|-----------------------|---------|-------------|--------------|---------|--------------------------|------------------------|-------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------|----------------|
| Gil-Montoya et al (2015) [37] | Spain   | 409         | Case-control | > 50    | Number of teeth present | 20–32, 10–19, 1–9     | DSM-IV                       | 1.76 (1.05–2.95)                | 1.25 (0.67–2.36)                                                                   | Age, sex, clinical attachment loss, oral hygiene habits, and hyperlipidemia   | 13         |
| Gatz et al (2006) [27]   | Sweden  | 3373        | Case-control | 59–107  | Number of teeth missing | All, Half, Has all teeth | Clinical diagnostic evaluations for dementia | 1.74 (1.35–2.24)                | 1.49 (1.14–1.95)                                                                   | Age, sex, education, mentally stimulating activities, physical exercise, parents’ social class, short adult height | 12         |
| Kondo et al (1994) [38]  | Japan   | 180         | Case-control | 43–89   | Number of teeth missing | More than half of the teeth, Total denture with no own teeth | DSM-III R                  | 1.90 (1.00–3.60)                | –                                                                               | –                                                                  | 11         |

Notes: DSM-IV The Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, DSM-III R Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised
Methods

Search strategy

We systematically searched electronic databases, including PubMed, EMBASE, Scopus and Web of Science, to identify studies that analyzed the association between tooth loss and dementia in adults from inception to March 2018 with the English language restriction using the key terms: dementia, Alzheimer’s, mild cognitive impairment, cognitive impairment, cognitive decline, cognitive disorder, memory disorder, memory disorder, tooth loss, oral health and dental care. References of relevant papers were also screened for additional publications and we did not retrieve unpublished studies. Predefined data-collection worksheets were employed for the assessment of each included paper. Any disagreement among authors was resolved by discussion until a consensus was reached.

Inclusion/exclusion criteria

For inclusion in this analysis, eligible studies should define tooth loss as one of the exposure interests, while incidence of dementia as one of the outcome of interests, and present original data or an crude and/or adjusted effect size, such as odds ratio (OR), hazard ratio (HR), or risk ratio (RR) of dementia with their 95% confidence intervals (CIs), or enough data to quantify the association between tooth loss and dementia risk. Different study designs were included. Abstracts from conferences, letters to the editor and reviews were excluded in the overall analysis. Animal studies were also excluded in this analysis. Moreover, concerning the quality assessment criteria, studies with a quality score of less than 5 points were not considered.

| Study ID                  | OR (95% CI) | % Weight |
|--------------------------|-------------|----------|
| Cross-sectional study    |             |          |
| Luo (2015)               | 3.65 (2.75, 4.86) | 6.55     |
| Peres (2014)             | 6.40 (3.40, 12.10) | 5.43     |
| Nilsson (2014)           | 9.20 (5.90, 14.30) | 6.10     |
| Wang (2014)              | 1.54 (1.13, 2.10)  | 6.49     |
| Park (2013)              | 2.69 (1.57, 4.64)  | 5.76     |
| Saito (2013)             | 27.33 (3.62, 206.21) | 1.84     |
| Lexomboon (2012)         | 2.10 (1.35, 3.25)  | 6.11     |
| Stewart (2007)           | 3.59 (2.36, 5.47)  | 6.17     |
| Subtotal (I–squared = 87.8%, p = 0.000) | 3.76 (2.37, 5.98) | 44.45    |
| Cohort study             |             |          |
| Takeuchi (2017)          | 3.83 (2.47, 5.93)  | 6.12     |
| Yamamoto (2012)          | 3.42 (1.05, 11.08) | 3.57     |
| Paganini–Hill (2012)     | 0.84 (0.67, 1.06)  | 6.67     |
| Arrive (2011)            | 1.35 (0.81, 2.25)  | 5.87     |
| Kim (2007)               | 1.38 (1.12, 1.69)  | 6.71     |
| Stein (2007)             | 2.69 (1.07, 6.73)  | 4.40     |
| Shimaazaki (2001)        | 5.20 (2.00, 13.10) | 4.33     |
| Subtotal (I–squared = 88.1%, p = 0.000) | 2.01 (1.24, 3.24) | 37.66    |
| Case–control study       |             |          |
| Gil–Montoya (2015)       | 1.76 (1.05, 2.95)  | 5.85     |
| Gatz (2006)              | 1.74 (1.35, 2.24)  | 6.62     |
| Kondo (1994)             | 1.90 (1.00, 3.60)  | 5.41     |
| Subtotal (I–squared = 0.0%, p = 0.969) | 1.76 (1.42, 2.18) | 17.88    |
| Overall (I–squared = 90.4%, p = 0.000) | 2.62 (1.90, 3.61) | 100.00   |

NOTE: Weights are from random effects analysis

Fig. 2 Pooled effect of crude results of tooth loss on dementia risk
Quality assessment
The quality of all selected studies was assessed using an adaptation of the Downs and Black criteria as described in previous systematic reviews [41–43]. From 27 original items in the checklist of the Downs and Black criteria, 17 were employed to accommodate the characteristics of observational studies, while other items specific for interventional randomization studies were removed. As recommended by Wehrmeister and colleagues [44], the total scores range from 0 to 18 points, given that each item scores one point, except for item 4 that can result in 0 (no), 1 (partially) and 2 (yes). Studies could be categorized with a quality score as: high chance of bias (0–5 points), moderate chance of bias (6–11 points) and low chance of bias (12–18 points) [41]. Two reviewers rated each study independently according to the above quality criteria, and discrepancies were discussed and resolved by consensus between referees.

Data extraction
We extracted data independently from each included study, using a standardized worksheet in particular concerning: name of first author, publication year, study region, study design, age, sample size, main exposures definition, crude effect size with their 95% CI, adjusted effect size with their 95% CI, and adjusted variables, follow-up time. We extracted the highest versus lowest effect size with their 95% CI of tooth loss number associated with dementia incidence for this analysis. The effect sizes with their 95% CI adjusted with the most confounders were extracted for the adjusted model [39]. Disagreements of methodology or result between investigators were solved by consensus.

Statistical analysis
The publications reported different measures of estimate effects including RR, OR and HR with their 95% CIs. Based on the assumption that the absolute risk of dementia was low and the person time of the exposed group was much smaller than that of the unexposed group, we did not make distinction between these size effects in this study. This way of pooling different measures of estimate effects has been used previously [45–49]. Meta-analyses were performed considering crude correlation between tooth loss and dementia risk and adjusted association between tooth loss and dementia risk. When various categories of tooth loss were shown, only the estimate comparing the most extreme categories was used for analysis as described in previous Meta-analyses [39, 41] Heterogeneity among studies was quantified using the Cochran’s Q test and chi-square ($I^2$) test. Heterogeneity was considered statistically significant with $P<0.05$ and random-effects model was used when heterogeneity was obvious ($I^2>50\%$) in this meta-analysis. Subgroup analyses and meta-regression were performed to explore the source of heterogeneity and it was conducted by the following subsets: study design (case-control or cohort or cross-sectional study), sample size, study region, and cognitive assessment. These approaches helped to identify whether the study characteristics mentioned above statistically affected estimate effects. We also assessed publication bias using both Begg-Mazumdar test and Egger’s regression test. When significant bias was found, we

### Table 4 Random-effect meta-analyses of tooth loss and dementia risk by subgroup and meta-regression analyses

| Studies with crude results | Number of estimates | Pooled OR and 95% CI | $P$-value | % heterogeneity explained |
|---------------------------|---------------------|---------------------|-----------|-------------------------|
| **Study design**          |                     |                     |           |                         |
| Cross-sectional           | 8                   | 3.76 (2.37–5.98)    | < 0.001   |                         |
| Cohort                    | 7                   | 2.10 (1.24–3.24)    | < 0.001   |                         |
| Case-control              | 3                   | 1.76 (1.42–2.18)    | 0.969     |                         |
| **Sample size**           |                     |                     |           |                         |
| ≥1000                     | 8                   | 3.26 (1.79–5.93)    | < 0.001   |                         |
| <1000                     | 10                  | 1.95 (1.51–2.52)    | 0.008     |                         |
| **Study region**          |                     |                     |           |                         |
| Asia                      | 9                   | 2.73 (1.83–4.07)    | < 0.001   |                         |
| Europe                    | 6                   | 2.57 (1.50–4.41)    | < 0.001   |                         |
| America                   | 3                   | 2.38 (0.57–9.91)    | < 0.001   |                         |
| **Cognitive assessment**  |                     |                     |           |                         |
| MMSE                      | 8                   | 3.12 (1.58–6.18)    | < 0.001   |                         |
| Others                    | 10                  | 2.38 (1.73–3.27)    | < 0.001   |                         |
| Total                     | 18                  | 2.62 (1.90–3.61)    | < 0.001   | –                      |
performed the trim and fill method to adjust for it. All analyses were completed with the Meta-analysis program software STATA 12.0 (StataCorp, College Station, TX, USA).

Results
The selecting processes for eligible studies were shown in Fig. 1. The literature search initially yielded 1574 papers, and 957 studies were duplicated. Abstracts from conferences, letters to the editor and reviews were excluded. Articles only with animal experiments or with repetitive data were removed. In addition, studies failed to provide enough data to quantify the association between tooth loss and dementia risk were also excluded. Finally, 21 studies published between 1994 and 2017 were identified for this analysis. Among all the studies, there were nine cross-sectional studies, nine cohort studies and three case-control studies and all the included studies were published in English. The main characteristics of studies were described in Tables 1, 2 and 3. Among these studies, nine were carried out in Asia, six in Europe and three in America. The total quality rating scores of included studies ranged from 11 to 16.

There were 18 studies provided crude estimates for the risk of dementia. The pooled crude results revealed that patients with fewer tooth remaining had higher incidence of dementia (OR 2.62, 95% CI 1.90–3.61), with significant heterogeneity among these studies ($P < 0.001$, $I^2 = 90.40\%$), as shown in Fig. 2. The random-effects model was used for the crude results. The heterogeneity was also explored by subgroup and meta-regression analysis for the crude model (Table 4). The study design

Fig. 3 Pooled effect of adjusted results of tooth loss on dementia risk
and sample size explained about 16.52% and 6.90% of the heterogeneity, respectively. There were 18 studies presenting adjusted estimates for the risk of dementia. The adjusted results remained significant when only adjusted results were pooled (OR 1.55, 95% CI 1.41–1.70), without obvious heterogeneity ($P = 0.13$, $I^2 = 28.00\%$; Fig. 3).

Both the Begg-Mazumdar test ($P = 0.11$) and Egger’s regression test ($P = 0.07$) showed no significant evidence of publication bias for all included studies in the crude model (Additional file 1: Figure S1 A-B). Although the Begg-Mazumdar test showed not statistically significance ($P = 0.15$), the Egger’s regression test ($P = 0.01$) revealed significant publication bias in the adjusted mode (Additional file 1: Figure S1 C-D). Therefore, the trim and fill method was conducted as a sensitivity analysis by imputing hypothetical negative unpublished studies conservatively to mirror the positive studies that cause the funnel plot asymmetry [50–52]. The symmetrical funnel plot appeared with the imputed studies and the pooled analysis remained significant, incorporating the hypothetical studies in the adjusted model (OR 1.50; 95% CI 1.36–1.64; $P < 0.001$; Fig. 4).

**Discussion**

Findings from this well-designed meta-analysis of 21 observational studies add to the accumulating evidence that tooth loss is a risk factor for dementia. Results from the crude model showed an overall 162% increase in dementia risk in adults, comparing individuals with high number of tooth loss to those with low number of tooth loss. We also observed an overall 55% increase in dementia occurrence risk in the adjusted model.

In the subgroup analysis by study design, the results remained significant in both the crude model and the adjusted model. However, it is possible to observe that in the crude model the association was not noted in European studies in the subgroup analysis by study region, while it was significant in Asia studies and American studies. These findings could be partially explained by the difference of healthcare systems and dental care access among different countries as described in the previous study [40]. Indeed, the great needs for dental care have been unmet in older adult population in many countries [9].

There is no known effective management for dementia and oral diseases are pretty common worldwide, particularly among older adults. Both dementia and tooth loss can result in significant impacts on people’s quality of life. Our findings have highlighted that adults living with higher number of tooth loss may have higher risk of dementia. In the general population, a general lack of knowledge of the importance of oral health partially account for the prevalence of tooth loss. Given the importance of tooth loss in the incidence risk of cognitive decline, oral health knowledge education programs and medical insurance policies are in urgent need among older adults population [9]. Oral health care and oral hygiene education are encouraged for both patients and their caregivers. Importantly, clinicians should be aware of this association, and oral examination should be a part of comprehensive assessments for those with high risk of dementia. Timely intervention of tooth loss may infuse new hopes for decreasing the incidence of dementia.

This study is not free of limitations. Firstly, we included cross-sectional studies in this analysis. In the light of such limitation, we conducted subgroup analysis by study design and the relationship remained significant in cohort studies, cross-sectional studies, and case-control studies. Secondly, different cognitive assessments were administered to determine participants’ cognitive function and various categories of the number of tooth

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**Fig. 4** Funnel plots without and with Trim and Fill. **A** Begg’s funnel plot with pseudo 95% CIs of the adjusted model. **B** Filled funnel plot with pseudo 95% CIs of the adjusted model.
loss were shown in studies. Finally, there was significant heterogeneity across studies in the crude model and publication bias in the adjusted model. Therefore, we used a random-effects model throughout to incorporate heterogeneity into the current analysis and we further identified possible sources of heterogeneity through meta-regression analyses. Additionally, the trim and fill analysis showed that the overall imputation did not alter the general results, indicating the results were robust to the possibility of unpublished negative studies. Regardless of the limitations, our review presents strengths that should be pondered. To the best of authors’ knowledge, this is the first well-designed systematic review with meta-analysis revealing both the crude and adjusted association between tooth loss and risk of dementia occurrence in adults. Secondly, the included studies from different settings demonstrate that the association between tooth loss and dementia risk is a global concern. Thirdly, the large number of sample size included in this analysis decreased the sampling error to a great extent.

Conclusions
This review provides valuable evidence for the positive association between tooth loss and increased risk of dementia in adults. The association remained significant in both the crude and adjusted models. These findings may implicate clinically on improving oral health and cognitive function. However, considering the inherent limitations of the included studies, further well-designed longitudinal studies exploring the direct and indirect relationship between tooth loss and dementia are urgently needed for a more definitive conclusion.

Additional file

Additional file 1: Figure S1. Beggs funnel plots and Egger’s publication bias plots, (A-B) Beggs funnel plot and Egger’s publication bias plot of the unadjusted model, respectively. (C-D) Beggs funnel plot and Egger’s publication bias plot of the adjusted models, respectively. (TIF 117 kb).

Abbreviations
AMTS: Abbreviated mental test score; BMI: Body mass index; CES-D: The Center for epidemiologic studies depression scale; CI: Confidence interval; CVD: Cardiovascular disease; DSM-III R: Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised; DSM-IV: The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; HR: Hazard ratio; IL-1: Interleukin-1; IL-6: Interleukin-6; MAC: Mid arm circumference; MMSE: Mini-Mental State Examination; OR: Odds ratio; RR: Risk ratio; TNF-α: Tumor necrosis factor –α; TMIG-IC: The Tokyo Metropolitan Institute of Gerontology Index of Competence

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Availability of data and materials
All data that have been used are reported in the manuscript.

Authors’ contributions

Study design: JL, WLF, and MJJ. Literature searching and initial screening of records: WLF, MJJ, BBG, and YMW. Abstract and article screening for eligibility: SNF, WL, and YQZ. Data extraction and risk of bias assessments: WLF and MJJ. Data analysis: YX, SWL, and YL. Manuscript preparation: WLF. Manuscript editing: JL, BBG, MJJ, and SHX. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests

The authors declare that they have no competing interests.

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