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Oral Health and Dementia: Causal Inference and Theoretical Mechanisms

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Abstract

Although studies have shown an association between oral health and dementia, causality and underlying mechanisms remain under debate. Reverse causality and unmeasured confounding factors, such as childhood cognitive function, raise questions about causality. Regarding theoretical mechanisms, essential oral functions such as eating and speaking are rarely discussed. The aim of this review was 2-fold: 1) to explain how recent epidemiologic studies tried to address these criticisms and 2) to suggest future research directions. To address reverse causality, studies used repeated surveys over time. Some studies considered the bidirectional relationship between oral health and dementia using appropriate methods. However, even in these studies, cognitive function prior to baseline was not incorporated. To infer the influence of unmeasured confounders, quantitative bias analysis using the *E* value is recommended, wherein the *E* value indicates the minimum strength of an unmeasured confounder needed to invalidate an observed association. Furthermore, methods that can ignore the effects of unmeasured confounding are good options, including fixed effect analysis and the instrumental variable method. However, few studies have applied these methods, yielding mixed results. Regarding mechanisms, although eating and speaking are essential oral functions, they have often been overlooked as potential mechanisms. These functions have a social aspect that facilitates interpersonal interactions and can reduce social isolation. The expert commission reported that social isolation in later life is 1 of the 14 modifiable risk factors for dementia. When we consider multilayered direct and indirect mechanisms of dementia throughout the life course in addition to the previously proposed mechanisms, such as periodontal inflammation, we find that poor oral health possibly increases dementia through social isolation via eating and speaking problems. In conclusion, based on causal inference studies and theoretical frameworks, oral health may be a modifiable risk factor for dementia. Methodologically and theoretically robust studies considering these points are needed to determine causality between oral health and dementia.

Keywords: epidemiology, causality, cognition, social Isolation, risk factors

Critiques of Causality between Oral Health and Dementia

The relationship between oral health and cognitive impairment, including dementia, has been reported (Larvin et al. 2023; Li et al. 2023; Lin et al. 2024). An umbrella review of 28 systematic reviews reported the association between severe deterioration of oral health and cognitive dysfunction (Lin et al. 2024). However, the causal nature of this relationship remains debated (Thomson and Barak 2021). The potential bidirectional relationship between oral health and cognitive function, along with unmeasured confounding factors such as childhood cognitive function, complicates causal inference. Regarding theoretical mechanisms, although biomedical mechanisms are often the focus, social aspects of oral functions, such as eating and speaking, are rarely discussed.

There is a possible reverse causality between oral health and cognitive function: cognitive decline leads to poor oral health behaviors that deteriorate oral health, rather than oral health affecting cognitive function. Individuals with cognitive impairment often experience difficulties in maintaining adequate oral hygiene, and this condition is associated with an increased risk of tooth loss (Peres et al. 2023). If both associations exist, this bidirectional relationship between oral health and cognitive function makes it challenging to determine the causal relationship between oral health and dementia (Peres et al. 2023).

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In epidemiologic studies of dementia not limited to dentistry, cognitive function in childhood may be an unmeasured confounding factor. Childhood cognitive function confounds the association between tooth loss and dementia (Thomson and Barak 2021; Thomson 2024). For example, lower cognitive function in childhood is linked to increased suboptimal dental health behaviors in adulthood (Thomson et al. 2019). Additionally, lower cognitive function in adulthood is associated with tooth loss and poorer oral health in older age (Kang et al. 2019). Since people with low cognitive function in childhood are also likely to exhibit lower cognitive function in old age, childhood cognitive function could be a confounding factor (Thomson and Barak 2021). This suggests that oral health might be an early marker of dementia rather than a direct cause.

Biological mechanisms are crucial in establishing causality. Regarding pathways between oral health and dementia, a systematic review of animal experiments summarized the mechanisms as reduced chewing stimuli, aggravation of nerve damage, and chronic inflammatory stress (Wang et al. 2022). Similar biological mechanisms have been proposed by which oral diseases influence cognitive function and other systemic conditions. Inflammatory stress is especially used as the mechanism of periodontal disease in systemic conditions. However, the results of intervention studies are not always clear. For example, a Cochrane systematic review of randomized trials on the treatment of periodontal disease for preventing adverse birth outcomes in pregnant women did not report a clear treatment effect (Iheozor-Ejiofor et al. 2017), which suggests that chronic inflammatory mechanisms by periodontal disease may not be linked to pregnancy outcomes. Although birth outcome is different from cognitive health outcome, these findings raise questions about the validity of biological mechanisms linking oral health to general health outcomes, including dementia.

Dementia is a major public health challenge in an aging world. Globally, the number of people with dementia is predicted to increase to 152.8 million in 2050 from 57.4 million in 2019 (GBD 2019 Dementia Forecasting Collaborators 2022). Dementia is characterized by impairments in memory, language, and behavior that interfere with activities of daily living (Robinson et al. 2015). Alzheimer disease is the most common subtype of dementia, followed by vascular dementia, mixed dementia, and Lewy body dementia. After several years of pathophysiologic changes, some individuals progress to mild cognitive impairment and eventually dementia (Sperling et al. 2011). The aim of this review was 1) to explain how recent epidemiologic studies tried to address these criticisms and 2) to suggest future directions for research on the relationship between oral health and dementia.

Challenge to the Reverse Causality between Oral Health and Cognitive Function

Research that attempts causal inference while considering the possibility of reverse causality uses repeated survey measurements over time. A longitudinal study examined the relationship between oral health and cognitive function among older people in England using data from 3 time points. This study reported the existence of a bidirectional relationship and a greater impact of oral health on cognitive function than that of cognitive function on oral health (Kang et al. 2020).

When a bidirectional relationship exists, a different problem arises in causal inference. If cognitive function between baseline and follow-up is a confounding factor between oral health and dementia and if it is affected by past oral health, it will be a time-varying confounding factor affected by previous exposure (Naimi et al. 2017). In this situation, adjustment of cognitive function during follow-up could cause overadjustment bias and/or selection bias. To resolve this problem, g methods are used for causal inference, including inverse probability-weighted marginal structural models, g estimation of a structural nested model, and the g formula (Naimi et al. 2017). G methods are less restrictive than standard regression models, which typically assume no feedback between time-varying exposures and time-varying confounders. G methods explicitly account for such feedback, making them more suitable for causal inference in longitudinal studies. Studies using these methods reported the association between natural teeth and cognitive function in adults in the United States (Matsuyama 2023); teeth, chewing difficulty, and xerostomia and dementia in older Japanese persons (Kusama et al. 2024); and chewing disability and cognitive impairment in Singaporean populations (Nascimento et al. 2024). These studies suggest that oral health affects future cognitive function despite bidirectional relationships.

These studies can examine the association between oral health and dementia only after the research begins. However, even in studies employing repeated measurements over time, cognitive function prior to the start of the first survey, such as childhood cognitive function, is not assessed or incorporated into the analytic models. The following section discusses causal inference in the presence of unmeasured confounding factors.

Unmeasured Confounding Factors and Causal Inference between Oral Health and Dementia

Difficulty in Causal Inference between Modifiable Risk Factors and Dementia

Causal inference methods in epidemiology are essential for examining relationships while accounting for confounding factors (Frieden 2017). Although randomized controlled trials (RCTs) are a well-known approach, they are often impractical or unethical. This is due to the random allocation of established treatments or harmful conditions, as well as the need for long-term follow-up, when studying the effects of oral health on dementia. RCTs are also infeasible for many of the potentially modifiable risk factors for dementia (Cribb et al. 2025), such as

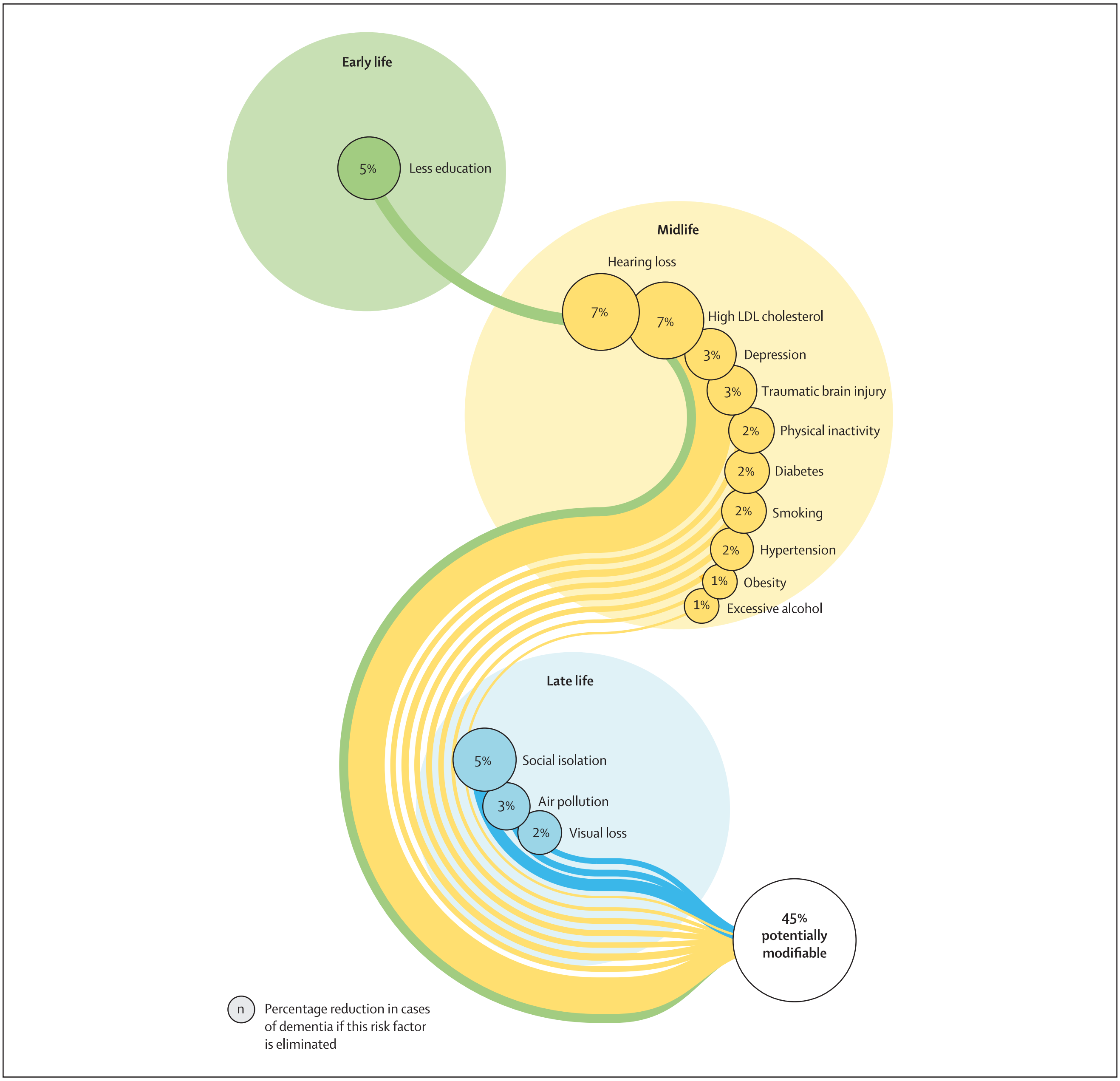

Figure 1. Potentially modifiable risk factors for dementia and their population attributable fraction. LDL, low-density lipoprotein. Reprinted from Livingston et al. (2024). Copyright 2024, with permission from Elsevier.

those reported by the Lancet Commission on dementia prevention, intervention, and care (Fig. 1): less education, hearing loss, a high level of low-density lipoprotein cholesterol, depression, traumatic brain injury, physical inactivity, diabetes, smoking, hypertension, obesity, excessive alcohol consumption, social isolation, air pollution, and visual loss (Livingston et al. 2024). Therefore, causal inference frameworks based on observational studies offer a feasible alternative to RCTs and have gained increasing attention (Frieden 2017). This section discusses the relationship between oral health and dementia using recent epidemiologic and statistical methods.

Unmeasured Confounding Factors and Causal Inference

In observational studies, causal inference is often conducted by using modeling approaches such as regression analysis or counterfactual frameworks (Naimi et al. 2017) that account for multiple confounding factors. Target trial emulation, which mimics

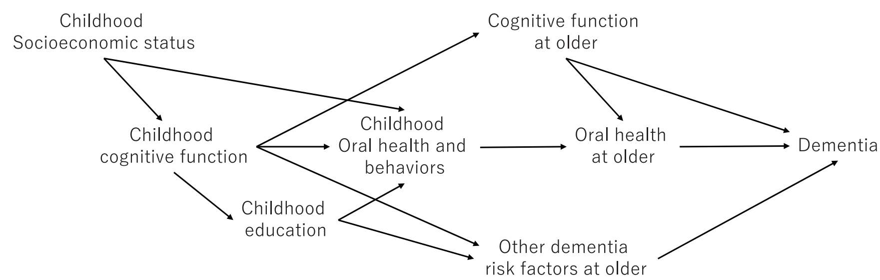

Figure 2. Possible directed acyclic graph for the association between cognitive function at childhood and older age, oral health, and dementia. Based on the proposed model for the association, rather than causality, between tooth loss and cognitive function by Thomson and Barak (2021), Figure 2 shows the directed acyclic graph for the association between oral health and dementia with childhood cognitive function as a confounding factor. If childhood cognitive function increases dementia risk only through factors in adulthood, the confounding effect of childhood cognitive function is considered by adjusting for the adulthood factors, even if childhood cognitive function is unmeasured. However, if childhood cognitive function directly influences dementia risk, consideration of childhood cognitive function as a confounding factor prior to the baseline is required in causal inference.

the structure of RCTs, is another recommended method in dementia research (Cribb et al. 2025). Some studies have applied modeling approaches to examine the relationship between oral health and dementia (Kiuchi et al. 2023; Matsuyama 2023; Kusama et al. 2024; Nascimento et al. 2024).

Even with these sophisticated causal inference methods, epidemiologic research on the relationship between oral health and dementia continues to face challenges due to unmeasured confounding. Based on the proposed model for the association, rather than causality, between tooth loss and cognitive function by Thomson and Barak (2021), Figure 2 shows the directed acyclic graph for the association between oral health and dementia, with childhood cognitive function as a confounding factor. If childhood cognitive function increases dementia risk only through factors in adulthood, the confounding effect of childhood cognitive function can be addressed by adjusting for the adulthood factors, even if childhood cognitive function is unmeasured. However, childhood cognitive function may directly influence dementia risk. In this case, consideration for childhood cognitive function as a confounding factor prior to the baseline is required in causal inference. In many studies on the relationship between oral health and dementia, childhood cognitive function is an unmeasured confounding factor. Such unmeasured confounding introduces bias even in the models with counterfactual frameworks (Cribb et al. 2025).

To infer the potential impact of these unmeasured confounding factors in the causal inference, quantitative bias analysis, such as use of the *E* value, is recommended. The *E* value indicates the minimum strength of an unmeasured confounder needed to invalidate an observed association (VanderWeele and Ding 2017). Such an evaluation is useful for estimating the magnitude of the association of unmeasured confounders that fully explain the observed association of oral health in adulthood with dementia. If the *E* value is large, the magnitude of the association of unmeasured confounding factors that fully explain the association between exposure and dementia is large; thus, the possibility of the existence of such unmeasured confounding factors is considered low.

Fixed Effect Analysis That Cancels the Effects of Childhood Characteristics

Even with those advanced modeling approaches, bias from unmeasured confounding factors is inevitable. RCTs can randomly assign even unmeasured factors and control for their confounding, a key advantage over observational studies. However, some opportunistic study designs can address unmeasured confounders: a natural experiment, mendelian randomization, the instrumental variables (IVs) method, regression discontinuity designs, interrupted time series designs, and difference-in-differences designs (Newman and Browner 2022).

Fixed effects analysis uses longitudinal panel data and contains the same concept as difference-in-differences designs. This method is unaffected by the effects of time-invariant factors consistent across different survey time points, even if these factors are unmeasured. In studies following adult participants, cognitive, health, behavioral, and social backgrounds in childhood do not change during the study period; therefore, their effects can be ignored.

A study using fixed effects analysis on Japanese older adults showed the association between a decline in oral status (tooth loss, swallowing difficulty, decline in masticatory function, dry mouth) and subjective cognitive complaints (Kiuchi, Kusama, et al. 2022). The result indicates that poor oral health in old age, independent of childhood cognitive function and other characteristics, leads to cognitive decline during the follow-up period.

However, there is still room for confounding. For example, if childhood cognitive function affects the speed of cognitive decline with age, it may act as a time-varying confounding factor. While fixed effects analysis can account for time-invariant confounding, its methodological limitations should be carefully considered.

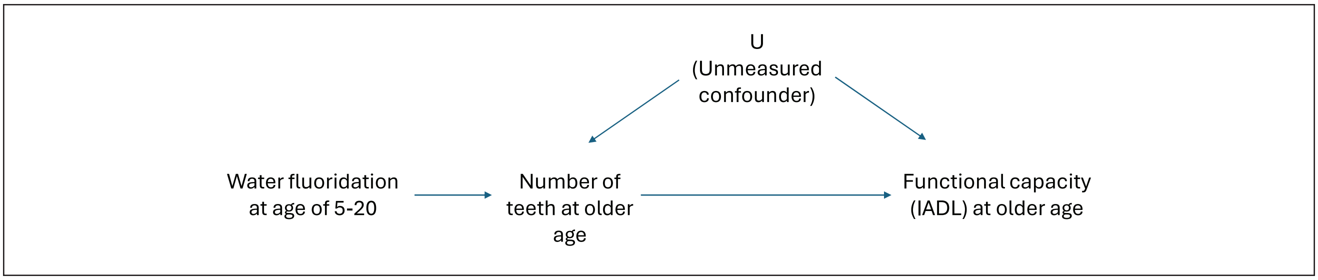

Figure 3. The concept of the instrumental variable (IV) method examines the relationship between the number of remaining teeth and functional capacity, with exposure to water fluoridation during childhood as an IV. This study in England (Matsuyama et al. 2021) examined the relationship between the number of teeth in old age and instrumental activities of daily living (IADL), which indicate physical and cognitive functional capacity. A valid IV needs to satisfy the following conditions: it predicts exposure, affects the outcome only through exposure, and is independent of confounding factors. Water fluoridation in childhood was used as an IV, as it was considered not to be affected by confounding factors and not to directly affect IADL (outcome). The IV predicted the number of teeth (exposure). This allowed estimation of the association between the number of teeth (exposure) and IADL (outcome) without the bias caused by confounding factors.

Controlling Time-Varying and Time-Invariant Confounding by the IV Method

The IV method is a quasi-experimental approach that can control for time-varying and time-invariant confounders, even if they are unmeasured. The IV concept is illustrated in Figure 3, with an example of an observational study (Matsuyama et al. 2021). That study in England examined the relationship between the number of teeth in old age and instrumental activities of daily living (IADL), which indicate physical and cognitive functional capacity.

A valid IV needs to satisfy the following conditions: it predicts exposure, affects the outcome only through exposure, and is independent of confounding factors. In the study, water fluoridation in childhood (IV) was used to predict the number of teeth (exposure). This allowed for the estimation of the association between the number of teeth and IADL (outcome) without the bias caused by confounding factors. If water fluoridation has the effect of improving or deteriorating children's cognitive function, irrespective of the number of teeth the IV assumptions would be violated. However, no reliable relationship has been reported between water fluoridation and cognitive function in childhood (Broadbent et al. 2015; Do et al. 2025).

According to the results of the study, 1 y more experience with water fluoridation between the ages of 5 and 20 y in England was associated with having 0.73 more teeth in old age, and having 1 more tooth in old age was associated with a 3–percentage point reduction in the probability of having any limitations in IADL (Matsuyama et al. 2021). These findings suggest that IADL, which reflect physical and cognitive functions, are affected by tooth loss independent of individual confounding factors such as childhood cognitive function.

Mixed Results and Need for Further Studies

As previously discussed, from a study design perspective, it is possible to account for unmeasured confounding factors. However, very few studies have applied these methods to examine the relationship between oral health and dementia. A study using an IV in England, similar to the one previously described, did not show an association between tooth loss and dementia (Santoso et al. 2024). The authors pointed out that the association between tooth loss and dementia in the previous observational studies was likely due to unmeasured confounding factors. Studies using mendelian randomization in which genes are used as IVs have reported limited or no associations between periodontal disease (Sun et al. 2020; Deng et al. 2024; Hu et al. 2024) or dental caries (Liao et al. 2023) and cognitive decline or dementia. In contrast, a systematic review of RCTs and cohort studies suggests that oral care, dental treatment, and oral motor exercise may positively influence cognitive function (Inamochi et al. 2024).

The mixed results may be explained by heterogeneity among studies: previous studies used different exposures and outcomes; the time frames between exposures and onset of outcomes also differed. Further studies that address the criticisms are necessary.

Mechanisms between Oral Health and Dementia: A Neglected Essential Function of Oral Health

While growing attention has been paid to biological mechanisms, such as chronic inflammatory stress, on health status, mechanisms related to essential oral functions, such as eating and speaking, are rarely discussed. Oral health is crucial for chewing, tasting, speaking, and smiling (Locker 1988). Therefore, oral health–related quality of life measurements include these broad essential functions (Tsakos and Allen 2021). A study showed that losing dentures in a natural disaster increased eating and communication problems in people with fewer teeth (Sato et al. 2015). These basic oral functions may indirectly raise dementia risk, but they are often ignored.

Social Isolation as a Direct and Indirect Risk Factor for Dementia

As a social determinant of health, social isolation is a growing public health issue (Holt-Lunstad 2022). A systematic review

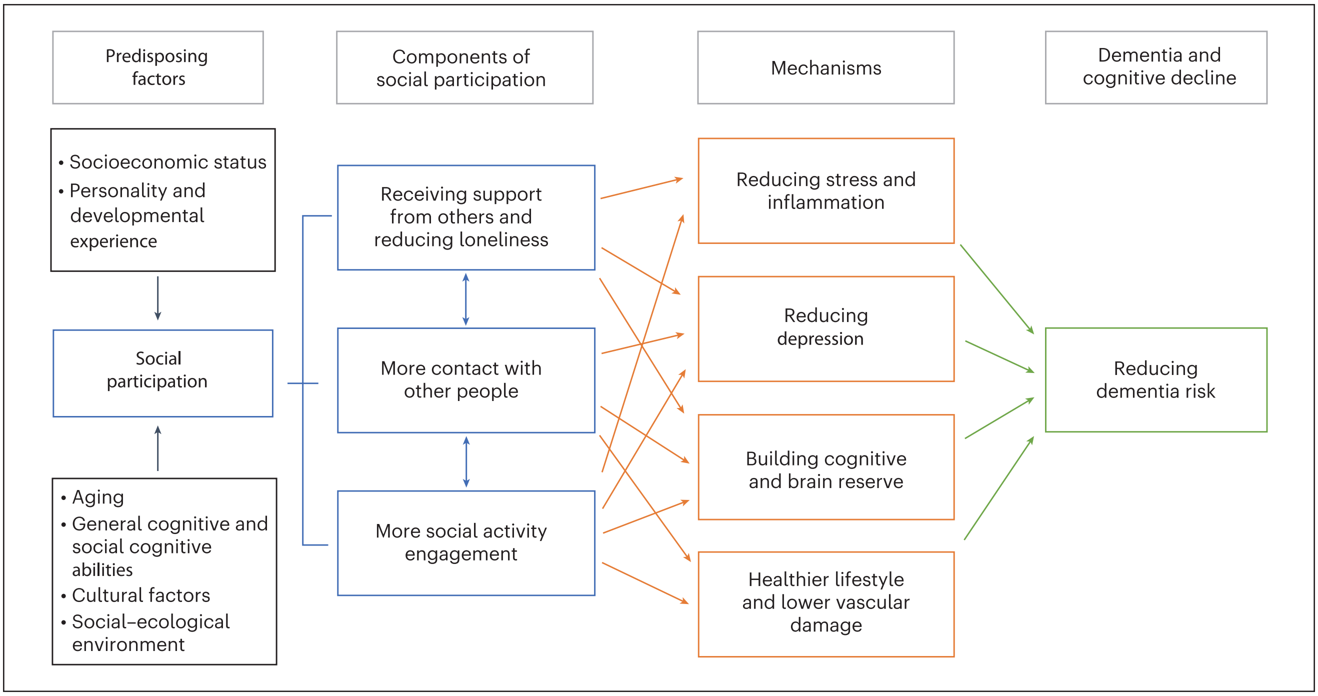

Figure 4. Potential mechanisms for the influence of social participation on dementia risk. Reprinted from Sommerlad et al. (2023). Copyright 2024, with permission from Springer Nature.

reported the association between oral health and both loneliness and social isolation (Hajek et al. 2022). Studies demonstrated the association of social relationships, including social isolation, social participation, social support, and networks, with mortality (Holt-Lunstad et al. 2010). As shown in Figure 1, social isolation is considered one of the modifiable risk factors for dementia (Livingston et al. 2024). Interventions that increase social participation also appear to improve cognitive function (Sommerlad et al. 2023).

There are complex mechanisms between social participation and dementia, and reductions in stress and inflammation, depression, unhealthy behaviors, and vascular damage, as well as built cognitive and brain reserve, are proposed as potential mechanisms, as shown in Figure 4 (Sommerlad et al. 2023). In addition, social isolation can be a mediator of other risk factors of dementia, such as hearing loss and visual loss, as listed in Figure 1. Hearing loss is thought to increase the risk of dementia directly by affecting brain function and indirectly by increasing social isolation (Lau et al. 2022). Social isolation is also considered a mediating pathway linking visual loss and dementia (Naël et al. 2019). To comprehensively understand the complex relationship between dementia and its risk factors, it is essential to consider the direct and indirect pathways.

Oral Health, Social Interactions, and Dementia

Oral health possibly affects dementia risk through social interactions. A systematic review reported the association between oral health and social isolation (Hajek et al. 2022). Through basic oral functions such as speaking, smiling, and eating (Tan et al. 2016; Haag et al. 2017), oral health is considered to relate to social isolation (Hajek et al. 2022). A recent longitudinal study reported the association of remaining teeth with social isolation (Abbas, Aida, Cooray, et al. 2023) as well as its related concepts, such as homebound status and social participation (Abbas, Aida, Kiuchi, et al. 2023; Cooray et al. 2023). These studies suggest that poor oral health may indirectly raise dementia risk by increasing social isolation due to difficulties in speaking and eating with others.

Eating has a social aspect that helps with interpersonal interactions. Older people with fewer teeth without any dental prosthesis are more likely to eat alone (Kinugawa et al. 2022). Eating alone increases the risk of weight loss (Kusama et al. 2022), and weight loss causes frailty (Fougère and Morley 2017). Frailty possibly increases the risk of dementia (Guo et al. 2022). An inverse association between protein intake and dementia has also been reported (Fujiwara et al. 2024). Poor diet and nutrition intake and the following effect on the central nervous system form another proposed mechanism between oral health and dementia (Qi et al. 2021; Thomson and Barak 2021; Li et al. 2023). Therefore, oral health possibly indirectly affects dementia risk by influencing social eating behaviors.

In summary, oral health may indirectly influence the risk of dementia by contributing to social isolation and frailty through speaking and eating problems. Mediation analysis can examine such indirect effects through intermediate variables. A cohort study employing mediation analysis has shown that having fewer teeth increases dementia risk through mediators relating

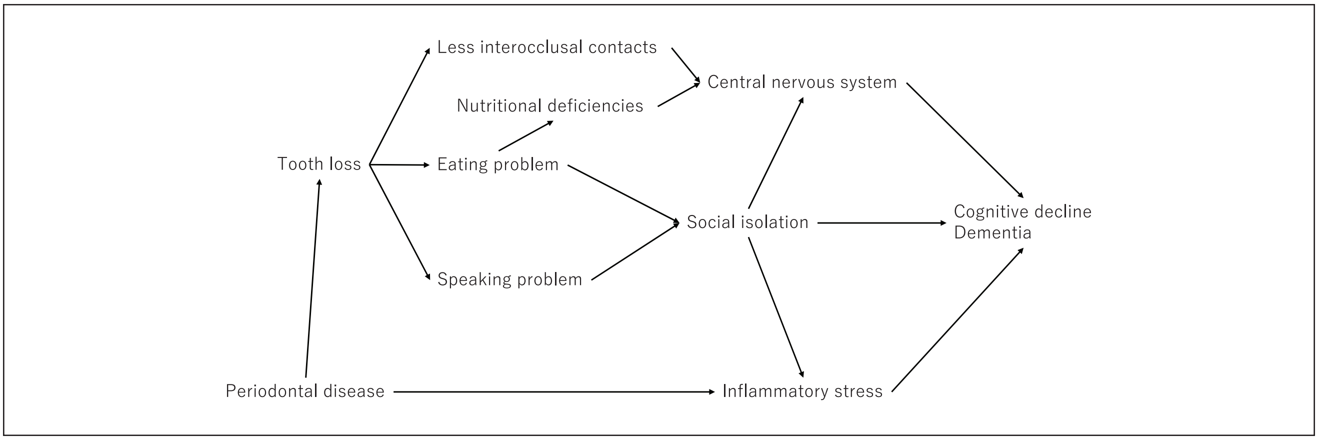

Figure 5. Potential mechanisms for the association between oral health and cognitive decline and dementia, considering social isolation.

to dietary intake and social interactions (Kiuchi, Cooray, et al. 2022). As oral health affects oral health–related quality of life (Tan et al. 2016; Haag et al. 2017), it is widely accepted that tooth loss makes speaking and eating more difficult, and this relates to social interactions. There is a need to expand the theoretical frameworks of the causal relationship between oral health and dementia to include the pathway relating to essential oral functions and social interactions, as summarized in Figure 5.

Oral Health as a Potentially Modifiable Risk Factor for Dementia

There is no single cause of dementia but rather a multilayered relationship of biomedical, behavioral, and social factors throughout the life course (Livingston et al. 2024). All other figures of this review show multilayered relationships. As shown in Figure 1, lower education is thought to be a risk for dementia early in life. Lower education may also increase dementia risk by influencing various health behaviors in adulthood, such as smoking, exercise, and diet (Letellier et al. 2021). Such factors in adulthood and later life are considered modifiable risk factors for dementia. Many public health interventions aim for behavioral change in adulthood and later life, and improving such modifiable behavioral risks is expected to prevent dementia (Livingston et al. 2024).

There is a critique that childhood cognitive function, not oral health, is the cause of dementia, with oral health being a marker rather than a cause (Thomson and Barak 2021). However, although childhood factors influence subsequent oral health behaviors (Thomson et al. 2019), oral health can be improved in later life. Improving oral health in adulthood can enhance diet and social participation, potentially reducing dementia risk. For example, an observational study suggests that social isolation may be reduced by the use of dentures after tooth loss (Abbas, Aida, Cooray, et al. 2023), and social participation may be sustained by the prevention of tooth loss (Cooray et al. 2023). Furthermore, an observational study reported that the use of dentures mitigates the association between tooth loss and cognitive impairment (Chou et al. 2024). Therefore, similar to other established modifiable risk factors for dementia (Livingston et al. 2024), oral health may represent a modifiable risk factor for this condition. As with other modifiable risk factors of dementia that change with aging, it is not easy to detect the effects of oral health on dementia throughout the life course. Because long-term intervention studies are difficult to conduct, it is necessary to accumulate observational study evidence, as described earlier.

Moreover, oral health possesses unique characteristics that are not seen in other risk factors. Oral diseases are one of the most prevalent diseases in the world (GBD 2021 Diseases and Injuries Collaborators 2024). The population attributable fraction (PAF) is a measurement that considers not only risk but also prevalence. A cohort study in Japan reported a higher PAF of teeth for mortality than other well-known risk factors, such as smoking, particularly among men (Nakazawa et al. 2023). In relation to oral and general health, the impact of oral health on dementia may be smaller than its impact on mortality (Kino et al. 2024). However, given the high prevalence of oral diseases, the PAF of modifiable risks, including oral health, should be examined in research on dementia risks.

Conclusion

Recent studies have employed improved designs and conceptual frameworks supported by sufficient data that address limitations of earlier research. However, epidemiologic studies with robust methodologies remain limited, and the results are mixed. In future research, it is essential to incorporate frameworks that consider the social aspects of oral health and its direct and indirect pathways to dementia risk and apply robust causal inference methods.

Author Note

During the preparation of this article, the first author utilized Grammarly and Copilot solely to correct grammatical errors and enhance readability in the early draft.

Author Contributions

J. Aida, S. Kiuchi, Y. Matsuyama, contributed to conception, data interpretation, drafted and critically revised the manuscript; K. Shirai, contributed to interpretation, critically revised the manuscript; M.A. Peres, contributed to conception, data interpretation, critically revised the manuscript. All authors gave their final approval and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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