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Review article

An umbrella review on the association between factors of oral health and cognitive dysfunction

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ABSTRACT

An increasing number of systematic reviews and meta-analyses have been published on the association between oral health and cognitive dysfunction, also known as oral-cognitive links. However, there is great diversity in the oral and cognitive factors included in these studies, with different opinions for clinical practice drawn from the evidence. To understand which oral and cognitive factors are involved in those associations, we conducted an umbrella review of 28 systematic reviews, including 12 meta-analyses, on oral-cognitive links. We found that (a) periodontal diseases, oral microbiome, and dementia were frequently studied, while other factors, such as mastication and mild cognitive impairment, were less commonly investigated, and (b) severe deterioration of oral health, such as severe periodontitis or extensive tooth loss, rather than the presence of oral diseases alone, was strongly associated with cognitive dysfunction. In conclusion, the diversity of oral and cognitive factors included in the review studies reflects the complexity of oral-cognitive links. Clarifying the factors helps to form evidence-based clinical advice for healthcare.

1. Introduction

Oral health has been widely accepted as a crucial aspect of systemic health in older adults (Patel et al., 2021). Cognitive dysfunction of pathological changes, including dementia, is a major challenge in healthcare worldwide. For example, the U.S. national prevalence of dementia in adults of 65 years and older, is estimated to be 10% (Manly et al., 2022). A close association exists between low cognitive function, poor oral health status, and a lower frequency of dental care utilization (Wu et al., 2007). In the past two decades, an increasing number of studies focused on the association between the deterioration of oral health, and worsen cognitive functions. The Nun Study reported an intriguing association between tooth loss and a higher risk of Alzheimer's disease (AD) (Stein et al., 2007), which was followed by multiple large-scale community-based studies. In addition to clinical studies, animal research contributed to elucidate the potentially cause-effect mechanisms underlying the association between oral and cognitive functions. Just recently, more research has targeted the possible neuroscientific, microbiological, and immunological mechanisms, underlying this 'oral-cognitive' association (Avivi-Arber et al., 2016; Dominy et al., 2019). Moreover, numerous systematic reviews/meta-analyses of human or animal research have been published in recent years to synthesize the findings and try to provide clinical advice for improving oral health and cognitive functions. Some researchers highlighted the importance to clarify the underlying mechanisms, before providing clinical suggestions (Lin, 2018; Thomson and

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Barak, 2021). At the same time, clinical implications were elaborated from other systematic reviews, which emphasized the role of oral factors (e.g., mastication or dental prosthesis) in preventing cognitive impairment (Ahmed et al., 2021; Chuhuaicura et al., 2019). Until now, there has been no consensus about how to translate these findings into clinical practice.

At present, the numerous systematic reviews published on the association between oral and cognitive factors primarily target a common question: *can we relate a certain oral health factor to a certain condition of cognitive status?* Many systematic reviews later, repeatedly reported a similar conclusion from earlier systematic reviews, i.e., worse oral health is associated with an increased risk of cognitive dysfunction. The diversity of systematic reviews may reflect the problem of 'overlapping meta-analyses' on the same topics (Siontis et al., 2013). For example, on the link between periodontitis and AD, the majority of the studies included in one review were also included in another review (Guo et al., 2021; Hu et al., 2021). However, a closer look into the clinical variables investigated in the systematic reviews revealed that these studies differed in how oral and cognitive factors were defined. Multiple terms of oral health and cognitive function, as shown in Table 1, were used in previous systematic reviews without a consistent definition. For example, some research restricted the term 'dementia' to patients with AD (Borsa et al., 2021; Elwishahy et al., 2021; Liu et al., 2023; Parra-Torres et al., 2023), while other research also included patients with other forms of dementia, e.g., vascular dementia (Asher et al., 2022; Larvin et al., 2023). Some research defined 'periodontal health' based on periodontitis, while other research considered tooth loss as an indicator of poor periodontal health (e.g., (Asher et al., 2022)).

Table 1
Definition of key terms in oral and cognitive factors.

Term	Definition (NLM)[a]
Periodontitis	'Inflammation and loss of connective tissues supporting or surrounding the teeth. This may involve any part of the periodontium. Periodontitis is currently classified by disease progression (chronic periodontitis; aggressive periodontitis) instead of age of onset.'
Periodontal disease	'Pathological processes involving the periodontium including the gum (gingiva), the alveolar bone (alveolar process), the dental cementum, and the periodontal ligament.'
Tooth loss	'The failure to retain teeth as a result of disease or injury.'
Mastication	'The act and process of chewing and grinding food in the mouth.'
Oral hygiene	'The practice of personal hygiene of the mouth. It includes the maintenance of oral cleanliness, tissue tone, and general preservation of oral health.'
Microbiota	'The full collection of microbes (bacteria, fungi, virus, etc.) that naturally exist within a particular biological niche such as an organism, soil, a body of water, etc.'
Oral health	'The optimal state of the mouth and normal functioning of the organs of the mouth without evidence of disease.'
Cognitive dysfunction	'Diminished or impaired mental and/or intellectual function.'
Dementia	'An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness.'
Alzheimer's disease	'A degenerative disease of the brain characterized by the insidious onset of dementia…'
Cognitive decline Cognitive impairment Mild cognitive impairment	Referred to as 'cognitive dysfunction'

[a] The definitions of terms are excerpted from the Medical Subject Headings (MeSH) database of the US National Library of Medicine (NLM).

Moreover, an oral factor may consist of a broad spectrum of conditions. For example, mild vs. severe periodontitis as well as limited vs. extensive tooth loss represents biologically and functionally divergent conditions. In sum, there is great diversity in the oral and cognitive factors included in the review studies on oral-cognitive links, with different opinions for clinical practice drawn from the evidence.

To investigate what oral and cognitive factors are involved in oral-cognitive links, we summarized the findings from recent systematic reviews by conducting an umbrella review, viz., a 'review of reviews', that focuses on integrating findings from systematic reviews (with or without meta-analyses), rather than evidence from primary studies (Aromataris et al., 2015; Fusar-Poli and Radua, 2018). The development of this umbrella review is further backed by the following rationale: First, the diversity of oral and cognitive factors in the review studies, which may contribute to inconsistent findings in meta-analyses, has not been fully evaluated. An umbrella review may provide a 'bird's eye view' of the convergences and divergences between the included systematic reviews. Second, oral health and cognitive dysfunction consist of a broad spectrum of conditions, as mentioned earlier. The umbrella review helps to differentiate the oral-cognitive links by stratifying the oral and cognitive factors. Third, there has been extensive investigation into the association between oral and systemic health in general. However, the studies did not show consistent findings regarding the association between oral health and cognitive dysfunction (Lavigne, 2022; Liu et al., 2022). An umbrella review that focuses on the oral-cognitive links is helpful to reconcile the inconsistency.

The current umbrella review focuses on three major aims:

1. Though various factors of oral health and cognitive dysfunction have been investigated in the review studies (Table 1), it has remained unclear if certain variables (e.g., periodontitis and AD) have been repeatedly investigated, while others were relatively neglected. Clarifying what and to what extent factors constitute oral-cognitive links is a fundamental step for further analysis of the complexity of the links. Therefore, our primary aim is to investigate what, and to what extent, oral and cognitive factors are involved in oral-cognitive links as analyzed in the systematic reviews/meta-analyses published in recent years.
2. Though some individual systematic reviews/meta-analyses have investigated the association between dementia and oral diseases of different severity (e.g., periodontitis (Larvin et al., 2023; Qiu et al., 2020) and tooth loss (Qi et al., 2021)), it has remained unknown how oral and cognitive factors link, when conditions of oral health and cognitive dysfunction are stratified into finer levels. Therefore, our second aim is to investigate whether advanced deterioration of oral health, such as severe periodontitis or complete edentulism, was strongly associated with cognitive dysfunction.
3. Thereafter, the third aim of the study is to revisit the limitations of current systematic reviews/meta-analyses and provide evidence-based suggestions on clinical practice and future research on the association between oral health and cognitive dysfunction.

2. Methods

2.1. Eligibility criteria of the systematic reviews

This umbrella review was conducted according to the guideline of the Joanna Briggs Institute (JBI) on umbrella reviews (Aromataris et al., 2015). The review protocol was registered at the international prospective register of systematic reviews (PROSPERO) (CRD42022366695). The systematic reviews included should meet the following list of criteria, according to the JBI reviewer's manual (Aromataris et al., 2015):

1. Types of participants: the included systematic reviews/meta-analyses need to investigate the human participants with various

types of cognitive dysfunction, or animal subjects that showed deficits in cognitive functions (e.g., spatial learning) (Table 1). It is noteworthy that animal studies that involved assessment of neurological changes (e.g., cellular loss of the hippocampus) related to cognitive functions (e.g., deficits in spatial learning) were included, because the experimental design better elucidated the potentially cause-effect mechanisms of the oral-cognitive links.

2. Interventions/phenomena of interest: the included systematic reviews need to investigate oral health status, which can be observational or modified by an experimental intervention (e.g., reduced mastication) (Table 1).
3. Outcomes: the included systematic reviews should focus on any of the "Key Terms" listed in Table 1. Notably, the current umbrella review only focuses on the oral and cognitive factors assessed using objective assessments or established criteria. Therefore, a review focusing on the outcomes of subjective evaluation, e.g., oral health-related quality of life (Ming et al., 2020; Wong et al., 2019), was not included.
4. The context/setting and types of systematic reviews were not restricted in the current umbrella review. However, due to the fast accumulation of primary studies on this topic, only the systematic reviews published since January 1st 2019 were included. The narrow range of publication years ensures that the systematic reviews comprised newer primary studies.

2.2. Search strategy

The literature search was conducted based on PubMed (as indexed with MEDLINE), the Cochrane Database of Systematic Reviews, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) with the combination of keywords derived from the terminology of oral health and cognitive impairment (see supplementary material (eTable1) for detailed search strategies). In addition, the systematic review or meta-analysis cited in previous review studies were manually included. An article was included only when the source journal is indexed by the databases above or enlisted in the Journal Citation Reports. Search and screening of eligibility was conducted independently by the authors (C-S Lin and T-C Chen) and a final list of included review studies was established by consensus (see Fig. 1 for a flow chart of the screening procedure).

2.3. Extraction of characteristics of the review studies

Data extraction was conducted independently by two of the authors (C-S Lin and T-C Chen). First, the information on the general characteristics and the design of review studies were extracted, according to the JBI manual (Aromataris et al., 2015) (Table 2): (1) the name of the first author, (2) the year of publication, (3) the type of review (a meta-analysis or a systematic review without a meta-analysis), (4) the databases being searched, (5) the range of publication years being searched, (6) the number of primary studies included, (7) the type of subjects (animals or humans), and (8) the limitation of age (for human subjects), (9) the study designs of primary studies, (10) the method of risk of bias assessment, and (11) the method of quantitative synthesis of primary evidence. Second, the information on research variables and the major results were extracted (Table 3 A): (1) the research variables related to oral health outcomes, (2) the research variables related to cognitive impairment, (3) the major conclusions, and (4) the evaluation of between-study heterogeneity and other potential factors confounding the conclusion.

2.4. Critical appraisal of the included review studies

We adopted A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) (Shea et al., 2017) for critical appraisal of the included systematic reviews. The assessment consists of 16 themes on potential biases according to the review methodology (Fig. 2).

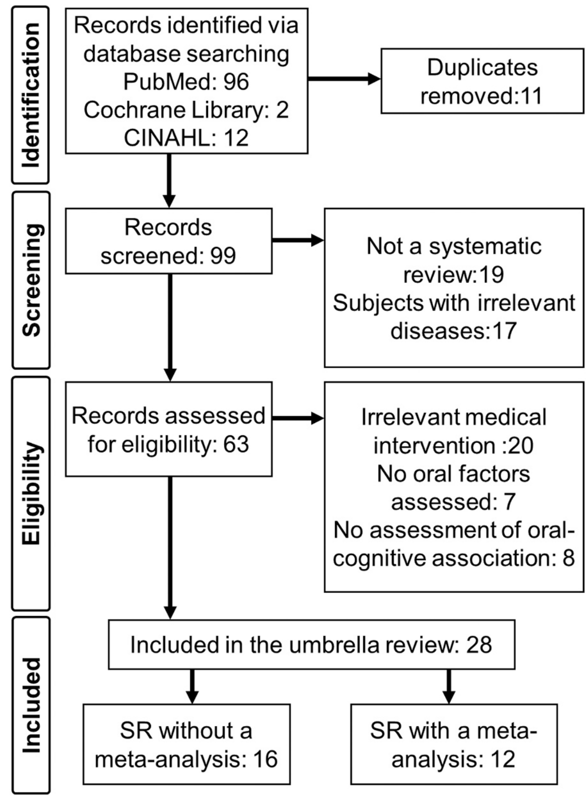

Fig. 1. The flow diagram of screening of eligible studies.

2.5. Data synthesis

At present, there has been no consensus about the statistical approaches for synthesizing findings from systematic reviews/meta-analyses (Aromataris et al., 2015; Belbasis et al., 2022; Fusar-Poli and Radua, 2018). Therefore, in the current study, we adopted qualitative, semi-quantitative, and quantitative approaches to investigate our research aims.

First, to understand which oral and cognitive factors are involved in oral-cognitive links, as analyzed in the systematic reviews/meta-analyses, we categorized the factors related to oral health into five domains (Table 3B): (a) tooth loss (TL), (b) periodontal diseases (PD, e.g. periodontitis of different degrees of severity), (c) oral function (OF, e.g. mastication), (d) oral health (OH, e.g. dental caries), and (e) oral microbiome (OM). We also categorized the factors related to cognitive dysfunction into six categories: (a) AD, (b) dementia or cognitive impairment not specific to AD (DEM), (c) mild cognitive impairment (MCI), (d) cognitive decline (CD), as assessed using clinical tools, in individuals without specific diagnosis of cognitive impairment (e.g., subjects from local community), (e) changes in specific cognitive functions (CF, e.g., language or spatial memory), as assessed using clinical tools, and (f) neurocognitive changes (NC, e.g. findings from cellular or brain activity). The included systematic reviews/meta-analyses were then tabulated according to the domains of the involved oral and cognitive factors. The analysis was performed for all 28 included systematic reviews/meta-analyses. The findings were visualized in a heatmap and analyzed qualitatively, identifying (a) the oral factor most/least commonly investigated, (b) the cognitive factor most/least commonly investigated, (c) the combination of oral and cognitive factors most/least commonly investigated.

Second, to investigate whether advanced deterioration of oral health was strongly associated with cognitive dysfunction, we analyzed 12

Table 2
Study design and methods of the included systematic reviews.

Source	Type	Database	Range of publication year		N	Subject (age)	Design	Quality / Bias assessment	Methods of quantitative synthesis	
Larvin 2023	M	Medline, Embase, Cochrane	database conception	2/2/2022	49	human	cross-sectional and longitudinal cohort studies	ROBINS-I	RR	RE
Liu 2023	M	PubMed, Embase, Cochrane Central Library, Scopus, ScienceDirect, WoS	first available date	5/2022	16	human	prospective cohort, case–control, cross-sectional studies	Based on previous research Lievense et al. (2004)	OR	RE
Parra-Torres 2023	SR	Medline, Latindex, SciELO, Cochrane	NR	4/30/2021	23	human / animal	experimental / observational studies	SYRCLE, NOS	-	-
Said-Sadier 2023	SR	PubMed, WoS, CINAHL	NR	9/2021	11	human	cohort, cross-sectional, case-control studies	NOS	-	-
Asher 2022	M	PubMed, Scopus, CINAHL, WoS, PsycINFO	NR	4/30/2022	47	human	longitudinal studies	Risk of bias in 5 domains, GRADE	OR/HR	RE
Dziedzic 2022	M	PubMed, Embase, Scopus, WoS, Cochrane, Clinical Trials, Google Scholar	1970	1/2021	17	human (≧45 y/o)	cohort studies, cross-sectional, case control studies	NOS	OR	RE
Mao 2022	SR	PubMed, Embase, Scopus, Google Scholar	NR	11/2021	26	human	cross sectional, cohort, case-control, post-mortem studies	NR	-	-
Wang 2022	SR	PubMed, Embase, SCI, ScienceDirect, OpenGrey	1/2020	9/2021	26	animal	experimental studies	SYRCLE		
Ahmed 2021	SR	PubMed, Cochrane, Google Scholar, Embase	2000	2019	15	human (>60 y/o)	interventional, human, questionnaire, cohort studies	CASP	-	-
Borsa 2021	SR	PubMed, Cochrane, Embase	2010	6/21/2021	5	human (>65 y/o)	clinical, longitudinal, transversal studies	NIH	-	-
Costa 2021	SR	PubMed, LILACS, SciELO, Science Direct, Scopus, WoS, Cochrane	NR	4/2020	9	animal	experimental studies	SYRCLE	-	-
Elwishahy 2021	SR	Cochrane, OVID Medline, PubMed, WoS, WHOLIS, Google Scholar	NR	8/31/2020	6	human	case-control, cohort stuies	NHLBI	-	-
Guo 2021	M	PubMed, WoS, Embase	NR	10/19/2020	20	human	observational studies	NOS	OR/MD	RE
Hu 2021	M	Cochrane, PubMed, Embase, CNKI, China Science and Technology Journal Database, WanFang, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform	inception	9/2020	13	human	observational studies	NOS, AHRQ	OR	RE/FE
Maitre 2021	SR	PubMed	1/2000	7/2021	27	human / animal	experimental or clinical studies (longitudinal, cross-sectional, or randomised studies)	NR	-	-
Qi 2021	M	PubMed, Embase, CINAHL, WoS, Cochrane	NR	3/1/2020	14	human	longitudinal studies	NOS, GRADE	RR	RE/FE
Zeng 2021	M	PubMed, Embase, PsycINFO, Cochrane, WoS	NR	11/8/2018	24	human	case-control, cohort, and cross-sectional studies	NOS	MD	RE/FE
Dioguardi 2020	SR	PubMed, Scopus	1990	NR	15	human / animal	in vitro experiments and clinical studies	NR	-	-
Maitre 2020	SR	PubMed	2000	6/2020	22	human / animal	clinical studies (longitudinal, cross-sectional, or randomised studies)	NR	-	-
Nadim 2020	M	PubMed, CINAHL, PsycINFO, SocINDEX, CNKI	NR	11/7/2018	12	human	a cohort or case–control study	NOS	RR	RE/FE
Piancino 2020	SR	PubMed, Embase, WoS, Scopus, OpenGray, GrayMatters	within the last 10 years	7/2020	28	animal	experimental studies	SYRCLE	-	-
Qiu 2020	M	PubMed, Embase, CNKI, VIP, WangFang	inception	1/2019	11	human	observational studies	NOS, AHRQ	RR/MD	RE/FE
Alvarenga 2019	M	PubMed, Scopus, WoS, LILACS, Cochrane, OpenGrey, Google Scholar	NR	2/2019	14	human	observational studies	Checklist of Fowkes and Fulton, (1991) GRADE	OR	RE
Chuhuaicura 2019	SR	PubMed, WoS, Scopus, Embase	NR	4/2018	9	human	cross-sectional, retrospective or prospective, cohort, case–control studies or clinical trials	CASP	-	-
Dioguardi 2019	M	PubMed, EBSCO, WoS	within the last 30 years	10/4/2018	9	human		NOS	HR	RE/FE

(continued on next page)

Table 2 (*continued*)

Source	Type	Database	Range of publication year		N	Subject (age)	Design	Quality / Bias assessment	Methods of quantitative synthesis	
Lauritano 2019	SR	PubMed, CINAHL, Cochrane	1990	2019	56	human (≧60 y/o)	cohort, case-control, cross-sectional studies, and randomized controlled clinical trials	NOS	-	-
Nangle 2019	SR	PubMed, Scopus, PsychINFO, WoS	NR	8/2018	23	human (≧55 y/o)	cross-sectional and longitudinal studies	NR	-	-
Nascimento 2019	SR	PubMed, Scopus, WoS, Cochrane, LILACS, OpenGrey, Google Scholar	NR	10/2018	8	human	observational studies	Checklist of Fowkes and Fulton, (1991)	-	-

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CASP, Critical Appraisal Skills Programme; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CNKI, China National Knowledge Infrastructure; FE, fixed effect; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; LILACS, Latin American & Caribbean Health Sciences Literature; M, meta-analysis; MD, mean difference; NHLBI, National Heart, Lung, and Blood Institute Study Quality Assessment Tools; NIH, the National Institutes of Health's study quality assessment tools; NOS; Newcastle-Ottawa scale; NR, not reported; OR, odds ratio; RE, random effects; ROBINS-I, Risk of Bias in Non-Randomised Studies of Interventions; RR, relative risk; SciELO, Scientific Electronic Library Online; SR, systematic review (without a meta-analysis); SYRCLE, Systematic Review Center for Laboratory Animal Experimentation; WHOLIS, WHO Library Database; WoS, Web of Science.

meta-analyses of oral-cognitive links, which used the statistical approach (e.g., a logistic regression model) to quantify the association between the factor of oral health and cognitive dysfunction. We adopted a semi-quantitative analysis with the following steps: (a) the odds ratio (OR) or hazard ratio (HR), which were the most frequently used estimates of the effect size of the association, and between-study heterogeneity (as indexed by I^2) were extracted, respectively for each meta-analysis. Notably, the association that was not statistically significant was excluded. (b) The meta-analytic findings (OR or HR estimates) were categorized according to the severity of oral health: the findings with the oral factors for severe periodontitis, moderate-severe periodontitis, and edentulism were categorized as the High-severity group. Other meta-analytic findings that did not specify the condition as high severity, or as a pooled analysis from all included primary studies, were categorized as the Non-specific group. (c) In addition, the meta-analytic findings were categorized according to the severity of cognitive dysfunction: the findings with the cognitive factor for dementia (including AD) were categorized in the DEM (dementia) group. In contrast, the findings with the cognitive factor MCI were categorized in the Non-DEM group.

2.6. Degree of overlapping between meta-analyses

Different meta-analyses may include the same primary studies, especially when they focused on the oral-cognitive links involving similar oral and cognitive factors. While some umbrella reviews excluded the meta-analyses of identical topics (e.g. (Kim et al., 2020)), the current umbrella review included multiple meta-analyses that focused on the same oral-cognitive link. Furthermore, we quantified the 'ratio of overlap' (RO) as the proportion of the number of the primary studies cited in meta-analysis A that was also cited in another meta-analysis B. It is noteworthy that the RO represents a bidirectional relationship between two studies A and B: a high RO(A,B) shows that a high proportion of the primary studies included in meta-analysis A is also included in another meta-analysis B. In contrast, a high RO(B,A) shows that a high proportion of the primary studies included in meta-analysis B is also included in another meta-analysis A. To investigate if the included meta-analyses have a high similarity in their included primary studies, we used a graph-based method to analyze the relationship between the meta-analyses according to the RO. Specifically, we identified the communities of the meta-analyses that are similar to each other due to the overlap of included primary studies (i.e., a higher RO). We first calculated the RO between two meta-analyses. Because 12 meta-analyses were included here, in total $12 \times 11 = 132$ scores of RO were calculated. Based on graph theory, a mathematic model of the connectional pattern of the 12 meta-analyses was established (Rubinov and Sporns, 2010). The graph consisted of 12 nodes (i.e., 12 meta-analyses) connected by 132 links. Subsequently, we analyzed if the graph formed different communities based on the inter-nodal connections by analyzing the modular architecture of the nodes (i.e., meta-analyses) (Rubinov and Sporns, 2010). The meta-analyses within a 'module' (or community of meta-analyses) may share a higher RO, suggesting that they included similar primary studies due to the similar focus on the oral and cognitive factors. In contrast, meta-analyses from two different modules may have a relatively lower RO because the divergent focuses on the oral and cognitive factors.

3. Results

3.1. Review studies eligible for the umbrella study

As shown in Fig. 1, 99 studies were extracted from three databases, after the removal of duplicates. In total, 28 studies were eligible for the umbrella study (Fig. 1), including 12 meta-analyses of human participants (Alvarenga et al., 2019; Asher et al., 2022; Dioguardi et al., 2019; Dziedzic, 2022; Guo et al., 2021; Hu et al., 2021; Larvin et al., 2023; Liu et al., 2023; Nadim et al., 2020; Qi et al., 2021; Qiu et al., 2020; Zeng et al., 2021) and 16 systematic reviews without a meta-analysis (Ahmed et al., 2021; Borsa et al., 2021; Chuhuaicura et al., 2019; Costa et al., 2021; Dioguardi et al., 2020; Elwishahy et al., 2021; Lauritano et al., 2019; Maitre et al., 2021; Maitre et al., 2020; Mao et al., 2022; Nangle et al., 2019; Nascimento et al., 2019; Parra-Torres et al., 2023; Piancino et al., 2020; Said-Sadier et al., 2023; Wang et al., 2022). See the supplementary materials (eTable2) for a list of the reasons to exclude studies.

3.2. Results of critical appraisal

The result of critical appraisal via AMSTAR 2 was summarized in Fig. 2 and supplementary material (eTable 3). In general, the included review studies fully or partially meet the criteria of most of the items of assessment, with several exceptions. Most of the systematic reviews did not provide a list of excluded studies ([7] in Fig. 2) for further examination of potential biases in study selection. Furthermore, most review studies did not fully evaluate the sources of funding of the included studies ([10] in Fig. 2), which are suggested as an item of data extraction by the PRISMA checklist (Page et al., 2021). Nevertheless, all the systematic reviews/meta-analyses have stated the PICO (population, intervention, control group, and outcome) elements for their eligibility criteria, and all the meta-analyses have stated the statistical approaches for data synthesis.

Table 3
(A) Clinical variables and major conclusions of the included systematic reviews.

Source	Oral-health variables	Cognitive-dysfunction variables	Conclusions	Additional notes
	(the following texts were all directly quoted from the abstracts or main text from the source articles)			
Larvin 2023	periodontal disease	cognitive disorders	'The prevalence and risk estimates of cognitive disorders in association with PD can be influenced by gender, the disease classification ofPD and its severity.'	
Liu 2023	oral bacteria	AD	'Current evidence moderately supports the association between oral bacteria and AD, while the association was strong when oral bacteria were detectable in the brain.'	
Parra-Torres 2023	oral bacteria's detection in the brain	AD	'The presence of bacteria in the brain is related to AD's pathological characteristics, suggesting an etiological oral- brain axis.'	
Said-Sadier 2023	periodontitis	neuroinflammation	'All the included studies show evidence of an association between periodontitis and cognitive impairment or dementia and Alzheimer's disease pathology.'	'...the mechanisms responsible for the association between periodontitis and dementia are still unclear and warrant further investigation.'
Asher 2022	poor periodontal health	cognitive decline and dementia	'Poor periodontal health and tooth loss appear to increase the risk of both cognitive decline and dementia.'	'… highly heterogenous, lacking robust methodology'
Dziedzic (2022)	periodontitis	age-related cognitive impairment (ACI)	'...there is a moderate statistical association between periodontitis and dementia, as well as Alzheimer's disease…'	'… the risk of bias in the evidence prevents conclusions being drawn about the role of periodontitis as a risk factor for age-related cognitive impairment.'
Mao 2022	oral microbiome	AD	'This review suggests that periodontal infection is associated with AD.'	'Additional large-scale studies with periodontal intervention and longitudinal follow-up are warranted to clarify the relationship between periodontal disease and AD.'
Wang 2022	the loss of occlusal support	cognitive decline	'The loss of occlusal support may lead to cognitive dysfunction through the reduction of chewing-related stimuli, aggravation of nerve damage, and long-term inflammatory stress.'	
Ahmed 2021	the influence of dental prostheses	cognitive functioning	'… dental prostheses have a very significant role in preventing the cognitive impairment and act as a protective factor in enhancing the cognitive function in patients with dementia-related diseases and neurodegenerative diseases'	
Borsa 2021	periodontal disease	AD	'The current review suggests an association between periodontal disease and Alzheimer's disease.'	
Costa 2021	infected with *Porphyromonas gingivalis* (*P. gingivalis*) or bacterial lipopolysaccharide (*Pg*-LPS)	affected by neuro-degeneration	'Infection by *P. gingivalis* and *Pg*-LPS administration appears to be in relation with the pathogenesis of AD …'	
Elwishahy 2021	*P. gingivalis*	AD	'… *P. gingivalis* bacteria play a role in the process of systemic inflammation which leads to cerebrospinal fluid inflammation and indirectly cause hastening of AD onset and progression.'	'… heterogeneity in the methodologies of measurement of AD and/or *P. gingivalis* and its virulence factors'
Guo 2021	periodontitis	dementia and cognitive impairment	'… there was an association between periodontitis and cognitive impairment, and moderate or severe periodontitis was a risk factor for dementia.'	
Hu 2021	periodontal disease	the risk of AD or MCI	'… PD was related to an elevated risk of AD and cognitive impairment, and that it should receive early intervention.'	
Maitre 2021	oral microbiome	AD	'Evidence for the impact of the oral microbiome on the pathophysiological and immunoinflammatory mechanisms of Alzheimer's disease is accumulating.'	
Qi 2021	tooth loss	risk of cognitive impairment and dementia	'… tooth loss was independently associated with cognitive impairment and dementia'	'… timely prosthodontic treatment with dentures may reduce the progression of cognitive decline related to tooth loss'
Zeng 2021	oral health	dementia	'Oral health was significantly poorer in people with dementia compared with controls.'	'Regular screening and effective treatment should be implemented for this population.'

(*continued on next page*)

Table 3 (*continued*)

Source	Oral-health variables	Cognitive-dysfunction variables	Conclusions	Additional notes
	(the following texts were all directly quoted from the abstracts or main text from the source articles)			
Dioguardi 2020	periodontal bacteria	the onset and progression of Alzheimer's disease	'… the bacterial load and the inflammatory process linked to periodontal disease can intensify inflammation at the level of the central nervous system, favoring the occurrence of the disease.'	
Maitre 2020	oral microbiome	mental health disorders (including AD)	'Studies argue for correlations between oral microbiota and Alzheimer's disease, autism spectrum disorders, Down's syndrome, and bipolar disorders.'	
Nadim 2020	periodontal disease	dementia	'PD could increase the risk of incident dementia. Preventing and treating PD could contribute to controlling the global epidemic of dementia.'	
Piancino 2020	experimentally altered mastication	trophism and function of the hippocampus	'The emerging role of chewing in the preservation of hippocampal trophism, neurogenesis and synaptic activity is worthy of interest…'	'More research is needed to clarify this topic.'
Qiu 2020	periodontitis	AD	'...periodontitis is associated with Alzheimer's disease…'	'… the number of existing studies is limited and more clinical evidences are needed to support the correlation between these two diseases.'
Alvarenga 2019	masticatory dysfunction	cognitive deficit	'Despite the low certainty in evidence, according to our MA, MD is positively associated with increased risk of CD.'	
Chuhuaicura 2019	mastication	the changes produced at brain level in adults associated with the brain blood flow	'Masticatory function may act as a protective factor in those patients with cognition impairment and neurodegenerative diseases…'	
Dioguardi 2019	oral health and the loss of dental elements	AD	'...patients suffering from Alzheimer's disease are characterized by a greater number of lost dental elements and general edentulism compared to the control groups.'	
Lauritano 2019	oral health/ periodontal disease	dementia/cognitive impairment	'Poor oral health is a common condition among the elderly with dementia. periodontal disease might contribute to the onset or progression of dementia.'	
Nangle 2019	oral health	specific cognitive abilities	'This systematic review provides evidence of an association between learning and memory, complex attention, and executive function with oral health in old age.'	
Nascimento 2019	periodontitis	cognitive decline	'...an association between periodontitis and cognitive decline is suggested.'	'The results should, however, be interpreted cautiously due to the limited number of studies.'

(B) Definition of the clinical variables of the included systematic reviews on human participants.

Source	Diagnosis / intervention of oral factors	Diagnosis criteria / Clinical assessment	Diagnosis of cognitive impairment	Diagnosis criteria / Clinical assessment
Larvin 2023 (Table 1)	periodontitis	clinical diagnoses, self-reported	dementia (AD,vascular dementia), cognitive decline	ICD-10 MMSE MoCA
Liu 2023 (Table 3)		oral bacteria sampled from gingival plaque, serum, saliva and etc.	AD	ICD-9, ICD-10, NIA-AA, NINCDS-ADRDA, DSM-IV, MMSE, CDR
Parra-Torres 2023		oral bacteria	AD	MMSE, CDT, ADAS-cog
Said-Sadier 2023 (Table 1)	periodontal disease	clinical diagnoses of periodontitis	dementia or neuro-inflammation (e.g., AD, cognitive impairment and MCI)	ICD-9, ICD-10, MMSE, MoCA, WAIS etc., factors related to neuro-inflammation
Asher 2022 (Supplementary Table 1)	poor oral health	clinical diagnoses of periodontitis, periodontal parameters (PPD, CAL, ABL), low tooth count/tooth loss	cognitive decline	MMSE, MoCA, etc.
			dementia	DSM-III R, DSM-IV, ICD-9, ICD-10, MMSE, etc.
Dziedzic (2022) (Table 1 and Table 3)	periodontitis	clinical and radiological parameters (PPD, CAL, ABL, BOP, CPI)	cognitive impairment, cognitive	ICD-9, ICD-10, DSM-IV, MMSE etc.

(*continued on next page*)

Table 3 (*continued*)

Source	Oral-health variables	Cognitive-dysfunction variables	Conclusions	Additional notes
	(the following texts were all directly quoted from the abstracts or main text from the source articles)			
			decline, dementia, AD	
Mao 2022 (Table 1)	periodontitis	periodontal parameters, inflammatory markers, PPD, CAL, teeth number, oral bacteria	AD	ICD-9, NIA-AA, DSM-V, NINCDS-ADRDA, ADA-cog, MMSE, CDR, CDT
Ahmed 2021 (Table 3 – Table 6)	use of dental prostheses	chewing ability, dental prostheses	elderly participants with or without cognitive impairment	MMSE, brain functions, etc.
Borsa 2021 (Table S2)	periodontal disease	clinical and microbiological criteria, periodontal parameters (PPD, BOP, ABL), oral bacteria	AD	ICD-9, ICD-10, DSM-IV, NINCDS-ADRDA, ADAS-Cog, MMSE
Elwishahy 2021 (Table 1 –Table 2)		*P. gingivalis* and related immunological factors	AD	DSM-IV, NINCDS-ADRDA, ADAS-Cog, MMSE, etc.
Guo 2021 (Table 1)	periodontitis	periodontal parameters (PPD, CAL, ABL, GI, CPI, CPITN, etc.)	dementia and cognitive impairment	ICD-9, DSM-III-R, DSM-IV, NINCDS-ADRDA, MMSE, MoCA, CDR, etc.
Hu 2021 (Table 1)	periodontal disease	clinical diagnoses, periodontal parameters (PPD, CAL, CPI)	AD	ICD-9, ICD-10, DSM-IV, NIA-AA, NINCDS-ADRDA
			MCI	ICD-10, NINCDS-ADRDA, MMSE, MoCA
Maitre 2021 (Table 1)	periodontitis	oral bacteria, periodontal parameters (PPD, CAL, PI)	AD	ICD-10, DSM-IV, MMSE
Qi 2021 (Appendix S4)	tooth loss	clinical examination, self-reported	dementia and cognitive impairment	DSM-III-R, DSM-IV, NINCDS-ADRDA, MMSE, MoCA, etc.
Zeng 2021 (Table 1)	poorer oral health	DMFT, DT, MT, FT, RT	dementia	ICD-9, ICD-10, DSM-IV, NINCDS-ADRDA, MMSE, CDR, etc.
Dioguardi 2020 (Table 3)		oral bacteria	AD	
Maitre 2020 (Table 1)		oral bacteria	AD, dementia, and cognitive disorders	
Nadim 2020 (Supplementary Table 1 –Table 2)	periodontal disease	clinical diagnoses, periodontal parameters (PPD, CAL, BOP)	dementia (AD, vascular dementia)	ICD-9, DSM-III, DSM-IV, NIA-AA, NINCDS-ADRDA
Qiu 2020 (Table 1)	periodontitis	periodontal parameters (PPD, CAL, PI, BOP, CPI)	AD	ICD-9, DSM-IV, NIA-AA, NINCDS-ADRDA, MMSE, MoCA
Alvarenga 2019 (Table 1)	masticatory dysfunction	tooth loss (no, mild, or severe)	cognitive deficits	DSM-III-R, MMSE, etc.
Chuhuaicura 2019 (Table 1 –Table 2)		chewing ability		cerebral blood flow, brain perfusion / oxygenation, MMSE
Dioguardi 2019 (Table 2 –Table 3)	tooth loss	missing teeth, edentulism	AD	
Lauritano 2019 (Table 5 – Table 6)	periodontitis, poorer oral health	DMFT, tooth loss, various factors related to periodontal and oral hygiene	dementia (including AD and MCI)	ICD-9, ICD-10, DSM-III-R, DSM-IV, NINCDS-ADRDA, MMSE, CDR
Nangle 2019 (Table 1)		various factors of tooth loss, periodontal parameters, oral hygiene		assessments of various aspects of cognitive functions
Nascimento 2019 (Table 1)	periodontitis	clinical and periodontal parameters (e.g., CAL, CPI)	cognitive decline	ICD-9, WAIS, MMSE etc.

Abbreviations: ABL, alveolar bone loss; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; BOP, bleeding on probing; CAL, clinical attachment loss; CD, cognitive deficit; CDR, Clinical Dementia Rating; CDT, Clock-Drawing Test; CPI, community periodontal index; CPITN, community periodontal index of treatment needs; DMFT, decayed, missing and filled teeth; DSM, Diagnostic and Statistical Manual of Mental Disorders; DT, decayed teeth; FT, filled teeth; GI, gingival index; ICD, International Classification of Diseases; MA, meta-analysis; MCI, mild cognitive impairment; -MD, masticatory dysfunction; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MT, missing teeth; NIA-AA, National Institute on Aging and Alzheimer's Association; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; *P. gingivalis*, *Porphyromonas gingivalis*; PI, plaque index; PPD, periodontal pocket depth; RT, remaining teeth; WAIS, Wechsler Adult Intelligence Scale

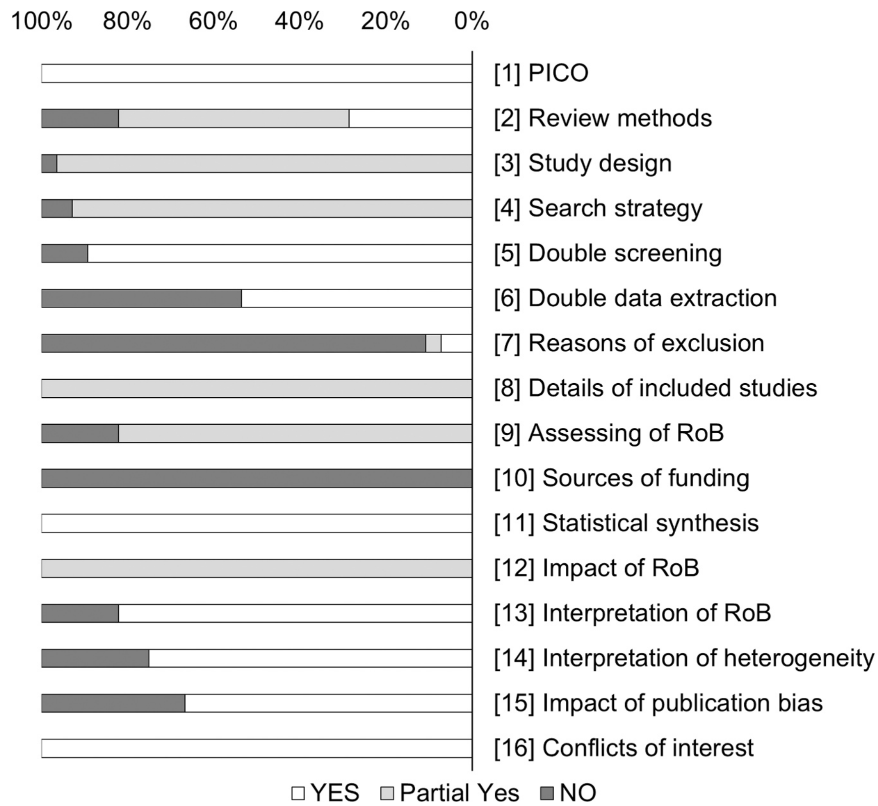

Fig. 2. Summary of the results of critical appraisal of systematic reviews. The number [1] to [16] represents the item of critical appraisal from AMSTAR 2 (Shea et al., 2017). The x-axis represents the percentage of the reviews that met (YES), partially met (Partial Yes), and did not meet (NO) the criteria of each item.

Table 4
Topics of oral-cognitive links. The studies with bold-type and italic labels represent a meta-analysis and an animal study, respectively.

	AD	DEM	MCI	CD	CF	NC
TL		**Asher 2022** **Qi 2021** **Dioguardi 2019** Lauritano 2019		**Asher 2022** **Alvarenga 2019** Lauritano 2019	*Wang 2022* Nangle 2019 *Piancino 2020*	*Wang 2022* *Piancino 2020*
PD	Mao 2022 Borsa 2021 **Hu 2021** **Qiu 2020**	**Larvin 2023** **Said-Sadier 2023** **Dziedzic 2022** **Asher 2022** **Guo 2021** **Nadim 2020** Lauritano 2019 Nascimento 2019	**Guo 2021 Hu 2021**	**Larvin 2023** **Said-Sadier 2023** **Asher 2022** **Dziedzic 2022** **Guo 2021** Lauritano 2019 Nascimento 2019	Nangle 2019	Said-Sadier 2023[b]
OF		Ahmed 2021		Ahmed 2021 **Alvarenga 2019**	*Piancino 2020*	Ahmed 2021[a] *Piancino 2020* Chuhuaicura 2019[a]
OH		**Zeng 2021** Lauritano 2019		Lauritano 2019	Nangle 2019	
OM	**Liu 2023** *Parra-Torres 2023*[c] Mao 2022 Borsa 2021 *Costa 2021* Elwishahy 2021 Maitre 2021[d] *Dioguardi 2020*[c]	Maitre 2020[d]				*Parra-Torres 2023*[c] *Costa 2021*

Abbreviations: AD, Alzheimer's disease; CD, cognitive decline; CF, changes in specific cognitive functions (e.g., language or spatial memory); DEM, dementia or cognitive impairment not specific to AD; MCI, mild cognitive impairment; NC, neurocognitive changes; OH, oral health; OF, oral function; OM, oral microbiome; PD, periodontal disease; TL, tooth loss.
[a]This systematic review included findings from human neuroimaging studies, which focused on brain activity.
[b]This systematic review included findings from human clinical studies, which focused on neuroinflammation.
[c]This systematic review included both animal and human research, while the majority of primary studies was animal research.
[d]This systematic review inclulded both animal and human research, while the majority of primary studies was human research.

3.3. Description of the included review studies

Table 2 shows the overall characteristics of the included reviews. All 12 meta-analyses focused on human participants. Among the non-meta-analytic systematic reviews, nine studies focused on human participants, three on animal models (Costa et al., 2021; Piancino et al., 2020; Wang et al., 2022), and four on both human participants and animal subjects (Dioguardi et al., 2020; Maitre et al., 2021; Maitre et al., 2020; Parra-Torres et al., 2023) (Table 2). The human studies mainly included observation-based primary studies (Table 2). 11 of the 12 meta-analyses have included more than 10 primary studies. Among the 16 systematic reviews without a meta-analysis, eight studies included more than 20 primary studies, while five studies included fewer than 10 primary studies (Table 2).

The main factors of oral health and cognitive dysfunction studied in the reviews and their major conclusions are listed in Table 3 A. In general, all the systematic reviews and meta-analyses identified the association between the oral and cognitive factors. Notably, different recently-published reviews reported very similar conclusions (e.g., (Borsa et al., 2021; Mao et al., 2022; Qiu et al., 2020) (Table 3 A). Nevertheless, the studies showed greater divergences in the interpretation and further implications of the findings. Some studies have concluded that the estimation should be interpreted with further considerations, including the impact of between-study heterogeneity and the risk of bias (e.g., (Asher et al., 2022; Dziedzic, 2022; Elwishahy et al., 2021; Nascimento et al., 2019)). While other studies highlighted potential clinical implications based on the findings (e.g., (Ahmed et al., 2021; Chuhuaicura et al., 2019; Nadim et al., 2020; Qi et al., 2021; Zeng et al., 2021)).

3.4. Synthesis of findings from the systematic reviews

To understand what oral and cognitive factors are involved in oral-cognitive links, as analyzed in the systematic reviews/meta-analyses, 28 reviews were included in the data synthesis (Table 2). The studies were tabulated according to the domains of the oral and cognitive factors involved in oral-cognitive links (Table 4) and visualized for an overview (Fig. 3). While most of the review studies focused on findings from human research, five studies focused on findings from animal research (Fig. 3 and Table 4). These studies focused on either the role of OM (Costa et al., 2021; Dioguardi et al., 2020; Parra-Torres et al., 2023) or the cellular changes of the brain (Piancino et al., 2020; Wang et al., 2022).

We found that some topics have been convergently investigated in multiple systematic reviews: (a) PD is the most commonly analyzed factor of oral health in the oral-cognitive links, while dementia was the most commonly analyzed factors of cognitive dysfunction. (b) The association between OM and AD was the most commonly analyzed oral-cognitive link. However, three studies of the OM-AD link were systematic reviews without statistical synthesis, with only one meta-analysis published. Most of the studies were based on animal research (Table 4). (c) The link between PD and DEM was also the most commonly analyzed oral-cognitive link (Fig. 3). Notably, all the eight studies published on this link were based on human participants (Table 4). In contrast, some associations were largely neglected in the systematic reviews. For example, the association between reduced oral functions (OF, i.e., mastication) was less investigated, except for its association with the biochemical and functional changes of the brain. There was also less evidence synthesized for the association between the oral microbiome and cognitive impairment other than AD (Fig. 3 and Table 4).

3.5. Synthesis of findings from the meta-analyses

To investigate whether advanced deterioration of oral health was strongly associated with cognitive dysfunction, 12 meta-analyses were

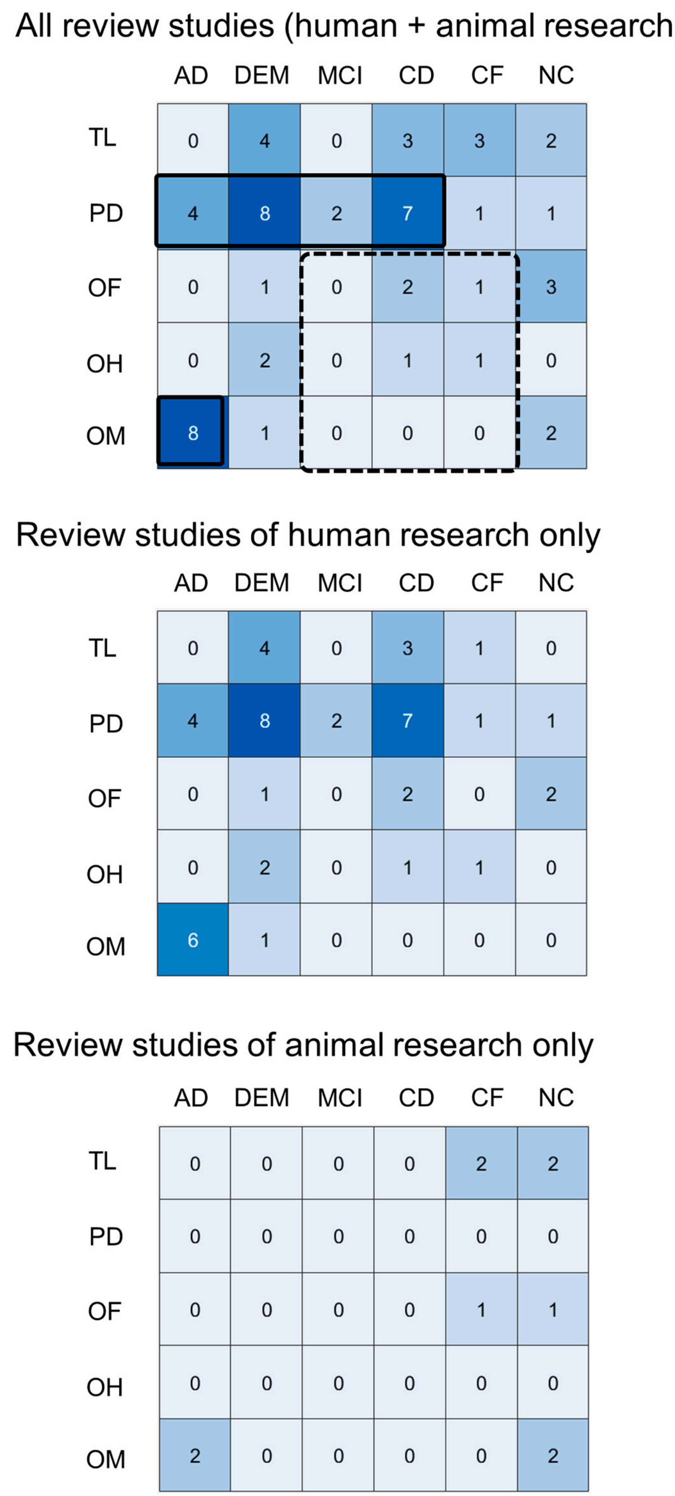

Fig. 3. A landscape view of the 'multiverse' of oral-cognitive associations investigated in the included systematic reviews. The heatmap shows the number of studies published for an association between a specific pair of oral and cognitive variables, respectively for all review studies, the studies of human subjects, and the studies of animal subjects. AD, Alzheimer's disease; CD, cognitive decline; CF, changes in specific cognitive functions (e.g., language or spatial memory); DEM, dementia or cognitive impairment not specific to AD; MCI, mild cognitive impairment; NC, neurocognitive changes; OH, oral health; OF, oral function; OM, oral microbiome; PD, periodontal disease; TL, tooth loss.

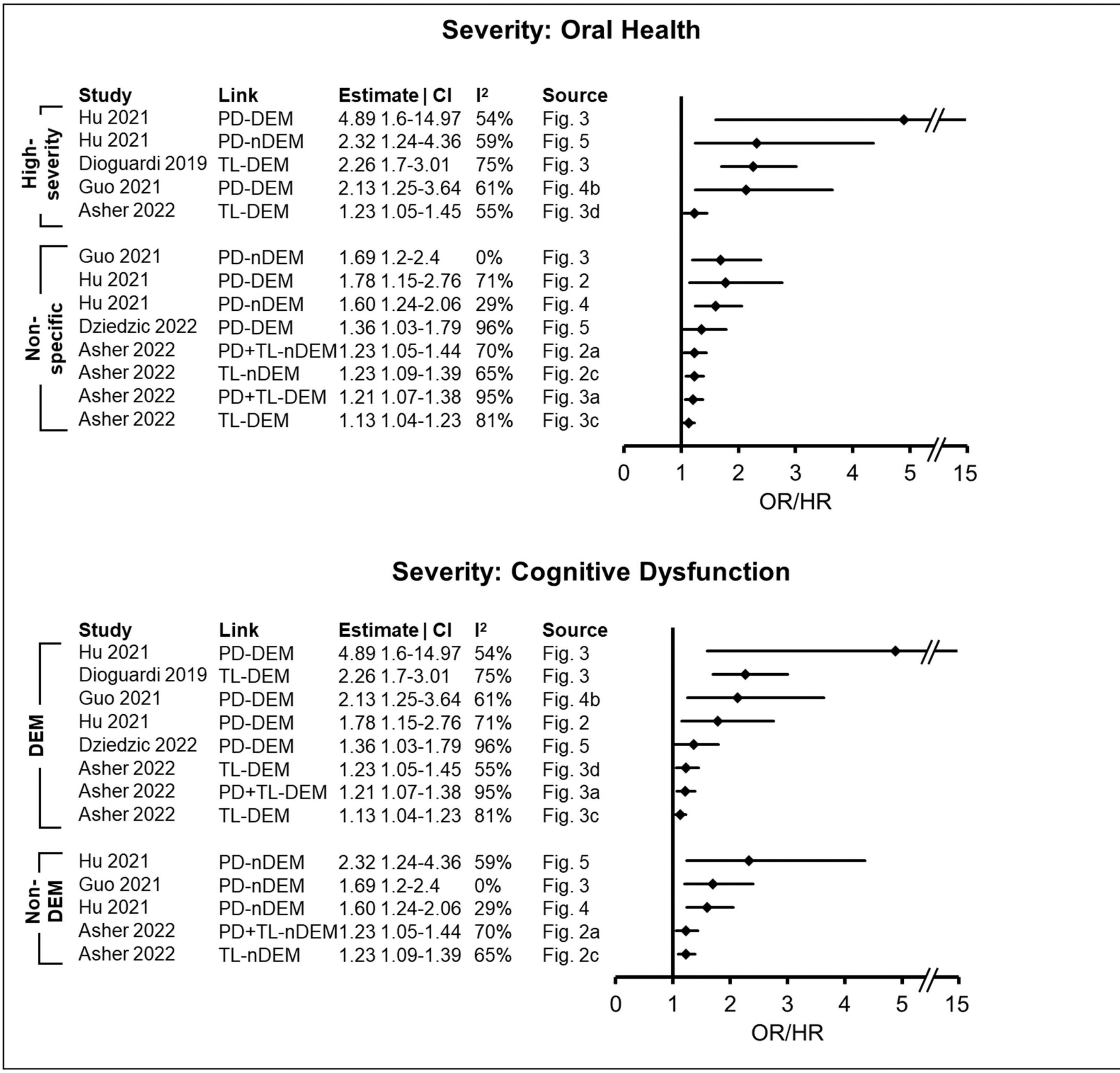

Fig. 4. Summary of the estimates of the associations between oral factors and conditions of cognitive health. DEM, dementia; HR, hazard ratio; OR, odds ratio; PD, periodontal disease; TL, tooth loss.

included in the data synthesis (Table 2). The quantitative findings from five meta-analyses of which the main estimates were relative risk or mean difference (Larvin et al., 2023; Nadim et al., 2020; Qi et al., 2021; Qiu et al., 2020; Zeng et al., 2021) were not analyzed here. One meta-analysis on the association between OM and cognitive dysfunction was excluded (Liu et al., 2023). In the High-severity group, four studies reported the association between cognitive dysfunction and high severity of oral health, including severe PD (Guo et al., 2021; Hu et al., 2021) and more extensive TL (i.e., edentulism or complete tooth loss) (Asher et al., 2022; Dioguardi et al., 2019). In the Non-specific group, four studies reported the association between cognitive dysfunction and PD/TL that were not specific to a high-severity oral condition (Asher et al., 2022; Dziedzic, 2022; Guo et al., 2021; Hu et al., 2021). The findings revealed that in the High-severity group, i.e., when only oral health of high severity was included in the meta-analysis, an higher OR (≧2) was reported (Fig. 4). However, larger between-study heterogeneity (>50%) was noted in this group. Additionally, when the findings were categorized according to cognitive dysfunction, we found five studies in the DEM group (Asher et al., 2022; Dioguardi et al., 2019; Dziedzic, 2022; Guo et al., 2021; Hu et al., 2021) and three studies in the Non-DEM group, including two meta-analyses that focused on MCI patients (Guo et al., 2021; Hu et al., 2021) and a meta-analysis that focused on patients with a lesser degree of cognitive deterioration (Asher et al., 2022). No significant discrepancy in estimates was observed between the two groups.

3.6. Analysis of the degree of overlap between included meta-analyses

The overlapping of primary studies between each pair of meta-analyses was tabulated in Table 5. The RO varied greatly between the

Table 5
The ratio of overlap (RO) of primary studies included in meta-analyses.

RO (A,B)[a]	Meta-analysis B											
Meta-analysis A	Larvin 2023	Liu 2023	Asher 2002	Dziedzic (2022)	Guo 2021	Hu 2021	Qi 2021	Zeng 2021	Nadim 2020	Qiu 2020	Alvarenga 2019	Dioguardi 2019
Larvin 2023		0%	41%	13%	13%	21%	21%	0%	10%	3%	8%	0%
Liu 2023	0%		0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Asher 2002[b]	64%	0%		8%	0%	12%	40%	0%	8%	0%	12%	0%
Dziedzic (2022)	71%	0%	29%		29%	57%	0%	0%	71%	43%	14%	14%
Guo 2021	25%	0%	0%	10%		40%	0%	20%	10%	20%	5%	25%
Hu 2021	62%	0%	23%	31%	62%		0%	8%	23%	31%	15%	15%
Qi 2021	57%	0%	71%	0%	0%	0%		0%	7%	0%	21%	0%
Zeng 2021[c]	0%	0%	0%	0%	20%	5%	0%		0%	15%	0%	15%
Nadim 2020[d]	57%	0%	29%	71%	29%	43%	14%	0%		43%	14%	14%
Qiu 2020[e]	11%	0%	0%	33%	44%	44%	0%	33%	33%		11%	33%
Alvarenga 2019[f]	33%	0%	33%	11%	11%	22%	33%	0%	11%	11%		11%
Dioguardi 2019	0%	0%	0%	11%	56%	22%	0%	33%	11%	33%	11%	

[a] RO(A,B) is the proportion of the number of the primary studies cited in meta-analysis A that was also cited in another meta-analysis B. For example, among the 20 primary studies included in the review by Guo 2021 (Meta-analysis A), 8 studies (40%) were also included in the review by Hu 2021 (Meta-analysis B).
[b] Only 25 out of 47 primary studies were included in meta-analyses.
[c] Only 20 out of 23 primary studies were analyzed for the comparison between dementia and control groups.
[d] Only 7 out of 12 primary studies were analyzed for the association between periodontal disease and dementia.
[e] One primary study was included in meta-analyses but not in the list of included studies. Only 9 out of 12 primary studies were included in meta-analyses.
[f] Only 9 out of 14 primary studies were included in meta-analyses.

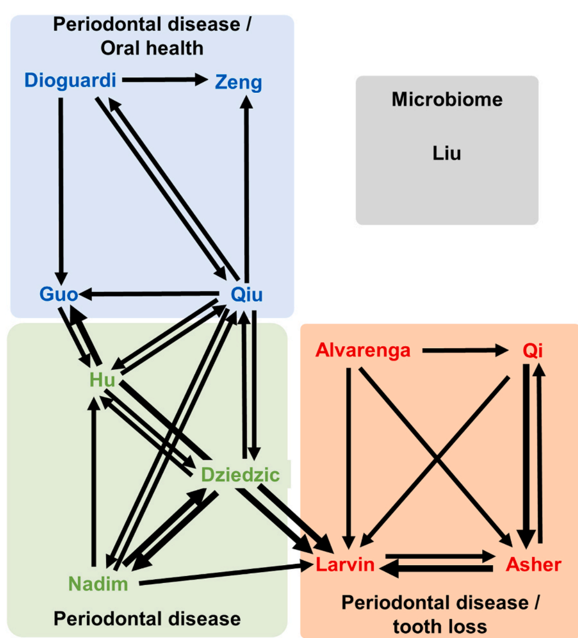

Fig. 5. The ratio of overlapping (RO) of the primary studies included in the meta-analyses. The thick and thin arrow lines represent an RO over 60% and an RO between 30% and 60%, respectively. For example, 71% of the studies included in the meta-analysis of Qi et al. (2021) are included in the one of Asher et al. (2022), while 33% of the studies included in the meta-analysis of Alvarenga et. al. (2019) are included in the one of Asher et al. (2022). For simplicity, the figure only presents an association with RO > 30% (please refer to Table 5 for the RO values). Further analysis of graph-based modularity showed four communities of the meta-analysis, which corresponded to the factors of oral health included: the meta-analyses focusing on periodontal health/tooth loss (orange), the meta-analyses focusing on periodontal diseases (PD) (green), the meta-analysis focusing on PD and poor oral health (blue), and one meta-analysis focusing on the oral microbiome (grey).
The arrow represents the percentage of the primary studies, as included in the source meta-analysis, included in the target meta-analysis. Note that the association is bidirectional between the source and the target meta-analysis.

12 meta-analyses included. Some meta-analyses of similar topics showed no overlap in the included primary studies (e.g., (Asher et al., 2022) and (Guo et al., 2021)). In contrast, some systematic reviews showed pronounced overlap (e.g., (Asher et al., 2022) and (Qi et al., 2021)). Chronologically, the earlier published reviews have a greater RO than the latter published ones (e.g., the RO between (Dziedzic, 2022; Nadim et al., 2020) and that between (Dziedzic, 2022; Larvin et al., 2023)), suggesting that some primary studies were repeatedly included in the studies focusing on a similar oral-cognitive link. In general, the RO showed a great variation between the meta-analyses.

Notably, the graph-based analysis of modularity revealed four modules or communities of meta-analyses, which showed a stronger association (i.e., RO) between each other. The organization of the communities corresponded to the involved factors of oral health included: the first community included the meta-analyses focusing on PD and TL (Fig. 5, orange). The second community included the meta-analyses focusing on PD (Fig. 5, green) and the third community included the meta-analysis focusing on PD and oral health (Fig. 5, blue). Notably, there were also strong associations between these two communities. Finally, an isolated community consisted of only one meta-analysis focusing on the oral microbiome (Fig. 5, grey).

4. Discussion

We conducted an umbrella review of 28 recently published systematic reviews, including 12 meta-analyses, on oral-cognitive links. We conducted qualitative analyses on the oral and cognitive factors included in the review studies and have the following major findings: First, among the oral factors, periodontal diseases and oral microbiome were most commonly studied, and dementia was the most commonly studied cognitive factor. Among the oral-cognitive links, the association between oral microbiome and AD as well as that between periodontal diseases and dementia, are the most frequently studied. Second, severe deterioration of oral health, such as severe periodontitis or extensive tooth loss, was strongly associated with cognitive dysfunction, rather than the presence of oral diseases alone. The findings are discussed in the following sections.

4.1. The missing pieces in the multiverse of oral-cognitive links

In recent years, the association between oral health and cognitive dysfunction has been studied extensively by an increasing number of systematic reviews/meta-analyses. However, our findings revealed that these review studies have a diverse focus on oral and cognitive factors. The diversity of oral and cognitive factors involved constitute a 'multiverse' of oral-cognitive links. Among these links, the association between OM and AD has been repeatedly investigated for evidence from both human and animal research (Fig. 3 and Table 4). The association between PD and dementia was also extensively investigated. However, we noticed that some links were under-presented in this multiverse, perhaps because of a lack of primary studies.

In terms of the cognitive factors, the association between MCI (and earlier stages of dementia) and OM was less explored, in comparison to AD. The lack of evidence may reflect the difficulty of differentiating MCI from other forms cognitive impairment (Asher et al., 2022). Because patients with AD have already shown a substantial loss of self-caring ability (including tooth-brushing), it may not be surprising that their cognitive dysfunction would further exacerbate oral hygiene and increase the risk of tooth decay, PD, and extensive TL. In contrast, clarifying the association between OM and the earlier stage of cognitive dysfunction (e.g., MCI) may be a more important issue because, at this stage, patients still preserve the ability to learn motor skills (Wu et al., 2016), and therefore further deterioration of oral health can be prevented. In terms of the oral factors, there were fewer studies focusing on OF, such as mastication. Several reviews were conducted for masticatory function (Fig. 3 and Table 4). The lack of evidence may reflect the fact that assessment of mastication, e.g., masticatory performance, was not part of the regular item of oral examination. In contrast, information on periodontal status and tooth loss is more available from regular check-ups. The human studies focused on investigating brain activation when participants were chewing vs. resting (Ahmed et al., 2021; Chuhuaicura et al., 2019). However, such a comparison only reflected the brain processing of normal mastication, rather than dysfunction. In contrast, the animal studies focused on the impact of extensive TL on mastication (Piancino et al., 2020; Wang et al., 2022). The studies successfully captured the deficits of masticatory function, but just presented the 'worse' scenario of masticatory dysfunction (due to tooth loss), which would happen in the late-stage of deterioration of oral health. In general, the systematic reviews/meta-analyses predominantly investigated the association between the late-stage conditions of deterioration of oral and cognitive health (e.g., periodontitis vs. AD).

Both oral health and cognitive functions change dynamically as age increases. For example, changes in masticatory cycles and performance may start earlier before patients evolved into edentulism (Ikebe et al., 2012; Peyron et al., 2017), and memory loss may happen ahead of more extensive deficits of cognitive functions. Therefore, a critical aspect of the oral-cognitive links is to examine the associations between early symptoms, which is, however, relatively neglected in current research. Our findings revealed that most of the review studies focused on the primary studies of both cross-sectional and longitudinal designs (Table 2). However, longitudinal studies, rather than cross-section ones, would better depict the progression of symptoms and clarify potential cause-effect mechanisms. In addition, though some researchers highlighted the effectiveness of dental treatment on cognitive dysfunction, we found only a few studies focusing on the issue. Confirmation of the effect of dental prosthesis (Ahmed et al., 2021) and a significant association between tooth loss without denture and dementia (Qi et al., 2021) were reported. The intervention-based findings should be a crucial target for analysis because it provides more clues about the effectiveness of treatment and potential cause-effect mechanisms. Another missing oral factor, but clinically critical issue, is orofacial pain. Because pain signifies tissue damage, it is sometimes regarded as merely a symptom of deterioration of oral health. However, pain also has its cognitive-affective component (Raja et al., 2020) and the difficulty to express pain may well be an important feature for patients with cognitive impairment (Delwel et al., 2018).

4.2. Revisiting the methodology of the review studies

A critical aspect of an umbrella review is to summarize and compare the review methodology between the review studies. Some common limitations are listed below. First, a great divergence existed between the definitions of the included oral and cognitive factors. For example, 'masticatory dysfunction' was indicated by tooth loss in human research (Alvarenga et al., 2019) or assessed by a gum-chewing test (Ahmed et al., 2021; Chuhuaicura et al., 2019). Some research defined poor periodontal health as having periodontitis and/or tooth loss (Asher et al., 2022), while some focused on periodontitis only (Hu et al., 2021) or considered both periodontitis and oral microbiome (Borsa et al., 2021) (Fig. 3 and Table 4). The divergence also existed for cognitive factors. Most studies of dementia primarily focused on AD. Only a few studies covered different types of dementia (e.g., vascular dementia) (Asher et al., 2022; Larvin et al., 2023; Nadim et al., 2020). Some research defined 'cognitive decline' as a lesser form of cognitive deterioration before dementia (Asher et al., 2022) but other research referred the term to patients with lower performance in cognitive assessments (Qi et al., 2021). Second, there was some inconsistency between the research questions and the eligibility criteria for study selection. For example, when the use of dental prosthesis (as an intervention) was investigated for its effect on cognitive health, a systematic review/meta-analysis should mainly include the comparison between the conditions with vs. without dental prostheses, rather than cross-sectional studies of elderly people (which may or may not wear dental prostheses). Third, inconsistency was found between the eligibility criteria and search strategy. For example, the study by Dintica et al. consisted of dementia-free subjects who received cognitive assessment (Dintica et al., 2018). The study is eligible for an investigation on cognitive decline, which refers to people with a lower cognitive performance by definition (Table 1) but not an investigation for assessing the risk of 'dementia'. Fourth, the divergences of the outcomes from different neurophysiological measurements should be carefully interpreted. For example, brain blood flow, perfusion, and blood-oxygenation-level-dependent signals represent different neurophysiological meanings.

In sum, the diversity in research methodology reflects the strong interdisciplinary nature of the oral-cognitive links. Therefore, the critical step of future research is to encourage cross-talk between experts in the fields of oral medicine, neuroscience, and geriatrics. Among the interdisciplinary experts, a consensus on research concepts and methods will expedite the translation between research findings and clinical application.

4.3. A refocus on finer stratification of oral and cognitive factors

While most studies focused on the associations between pathological conditions, such as periodontitis and AD, the deterioration of oral and cognitive health showed a great difference in severity. In terms of oral factors, we found that severe PD and extensive TL showed a stronger association with dementia (Fig. 4). The findings highlight the importance of a finer stratification of the clinical variables. For example, the examination based on a standardized periodontal checkup (e.g., clinical attachment loss), rather than an overall diagnosis (e.g., the presence of periodontitis), would provide more information for depicting the oral-cognitive links. In terms of cognitive factors, we did not observe a substantial difference in oral-cognitive links between dementia and non-dementia impairment (Fig. 4). However, such dichotomy (dementia vs. non-dementia) may be too coarse because, at the earlier stage of dementia, patients may have already presented deficits in some aspects of cognitive functions (e.g., memory loss), before a full-scale deterioration (Bennett et al., 2002). In other words, the current systematic reviews/meta-analyses cannot explain whether oral health is important to certain cognitive functions. In fact, we found very few studies focused on the different aspects of cognitive functions (e.g., (Nangle et al., 2019)) (Table 4).

It is noteworthy the extent of detrimental effects of normal aging and pathological changes may vary among individuals. Individuals with cognitive resilience, defined as 'toughness or capacity to recover quickly from difficulties', preserve cognitive functioning even at a very old age (Aiello Bowles et al., 2019). Until now, most of the primary studies and reviews consider individual cognitive conditions as discrete categories (e.g., cognitively impaired or healthy). However, even for healthy people there may show an age-related decline in cognitive functions, and not every cognitively impaired patient would progress into more a severe status. Without a finer stratification of the oral and cognitive conditions, it would be difficult to disentangle the dynamic interaction between oral health and the progression/preservation of cognitive functions.

4.4. Clinical considerations for dental practitioners

By converging the findings from the umbrella review, we summarized clinical considerations for dental practice:

1. Extensive deterioration of oral health, including complete edentulism and/or severe periodontitis, consistently showed a strong association with dementia (Fig. 4). Moreover, severe tooth loss and periodontitis have posed a great burden to geriatric health (Kassebaum et al., 2014a; b). Therefore, prevention and identification of the late-stage deterioration of oral health should still be the primary task of dental examination for older people. Especially, in the community and long-term care institutions, the awareness of oral diseases should be raised for caretakers of older people so that further deterioration can be prevented in time (Griffin et al., 2012).
2. Our findings revealed that multiple oral factors contribute to the oral-cognitive links. In oral health, the combination of clinical and laboratory-based assessment contributes to personalized diagnosis and treatment (Belibasakis et al., 2019; Mira, 2018). Therefore, a more comprehensive examination combining assessments of periodontal tissue, dentition, mastication, and microbiome, would provide more information for evaluating the risk of dementia. In contrast, clinical prediction of cognitive dysfunction based on a single oral health-related factor (e.g., the presence or absence of periodontitis) should be made with great caution.
3. In terms of dental treatment, the goal of dental intervention should be clarified to older adults by focusing on the main therapeutic effects, to avoid unnecessary treatment for vulnerable older people (Thomson and Barak, 2021). For example, prosthodontic treatment is advised to patients due to the benefits of improving oral function (e.g., mastication) and oral health-related quality of life, which has been backed by strong meta-analytic evidence (Gerritsen et al., 2010). Mastication was also known to change cerebral circulation (Hasegawa et al., 2007; Ono et al., 2007); however, the benefit of more mastication to 'prevent cognitive impairment' would require more primary studies with proper experimental design and synthesis of the evidence. An over-emphasis on the so-called positive effect of the dental intervention on cognitive dysfunction is misleading to patients by confusing the major benefits of treatment (Pihlstrom et al., 2018).
4. Due to the complexity of oral-cognitive links, the translation from research findings to clinical practice requires interdisciplinary collaboration between both medical and dental professionals (Lobbezoo and Aarab, 2022). On the one hand, dentists should be aware that brain and behavioral factors play a key role in oral health (Lin, 2021); on the other hand, physicians, including neurologists, should recognize that oral diseases and functions are not isolated from systemic health and need to be considered (Shenkin and Baum, 2001).

In sum, we suggest that both screening for severe deterioration at home and in institutions, and a comprehensively functional and microbiological examination at the clinics, are both critical to assess the oral-cognitive links. A precise examination of the oral and cognitive factors should be the premise of any active intervention for preventive purposes.

4.5. Future directions of research on oral-cognitive links

Despite numerous studies on the oral-cognitive links, the current umbrella review shows that several critical questions remain unanswered. Further investigation on the following questions – which have not yet been widely explored – may facilitate an evidence-based practice on dental and geriatric patients.

(a) *What are the roles of behavioral and systemic factors in the links?* Both oral and mental health are associated with behavioral and systemic factors, which were not fully discussed in the review studies. For example, the roles of nutrient intake and daily activities in the oral-cognitive links have been proposed in earlier research (Weijenberg et al., 2011). Furthermore, both oral and mental health are associated with one's physical health at the systemic level (Dibello et al., 2022) and it would be reasonable to hypothesize that other deficits, such as cardiovascular diseases (Abete et al., 2014) and frailty (Parisius et al., 2023), may play a role in the links. In older adults, the connection between oral, cognitive, and systemic health would require further investigation.

(b) *Can we predict the long-term association between oral health and cognitive status?* While most of the review studies suggested the association between oral health and cognitive dysfunction, it remains unknown if the evidence helps clinicians establish a predictive model to forecast the deterioration of oral health or cognitive function in the long run. Most of the primary studies and systematic reviews focused on cross-sectional data or longitudinal data with a relatively short term. Therefore, the dynamic relationship between oral and cognitive health, which spans from childhood to older age (Thomson and Barak, 2021), was hardly assessed. It should be noted that the cause-effect relationship between oral and cognitive factors may be more complicated than a single-directional effect (Kang et al., 2020; Lin, 2018). For example, changes in the oral microbiome may influence cognitive health, and deteriorated cognitive functions would compromise one's ability to clean mouth and lead to poor oral hygiene, which potentiates oral bacteria (Lin, 2021). Such a dynamic interaction between oral and cognitive factors can be fully investigated only when data from long-term observation is available.

(c) *How much is the effect size of oral rehabilitation on changing cognitive status?* A critical question that remains unanswered is the causality underlying the oral-cognitive links. Individuals who are cognitively resilient would preserve their functions even with a disorder or old age. The resilience is linked with individual reserve and maintenance of multiple cognitive and brain factors (Stern et al., 2020). It would be critical to assess if good oral health plays a role in the reserve against cognitive dysfunction. To assess the effect size (if any) of these oral factors, more evidence from intervention-based clinical trials is required. For example, to assess the effect of dental prosthesis on cognitive functions and neuroplasticity of the brain, an assessment should be performed before and after the intervention, with a balanced comparison between different treatment groups (Hedberg et al., 2021; Tan et al., 2020). An intervention-based design would offer an estimate of the effect size of the dental intervention, which is essential for dentist-patient communication and decision-making.

4.6. Conclusion

The umbrella review revealed a great diversity of factors of oral health and cognitive dysfunction included in the review studies. Such diversity reflects the complexity of oral-cognitive links, many of which focused on the late-stage deterioration of oral and cognitive functions. Clarifying the oral and cognitive factors would avoid misleading conclusions and help to form evidence-based clinical advice for healthcare.

CRediT authorship contribution statement

CSL and TCC conceptualized the study; CSL and TCC designed the protocol; CSL and TCC carried out the screening, data extraction and risk of bias evaluation; CSL, TCC, MCV, FL, MT, and JLF performed and interpreted the results of analyses; CSL drafted the initial version of the article and coordinated and supervised the overall project; all authors critically revised the manuscript and approved its final version. CSL and TCC had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of Competing Interest

None.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2023.102128.

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