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Role of oral microbiota in Alzheimer's disease: A systematic review of clinical studies

Qiujun Piao

Oxford International College, Threeways House, 36 George St, Oxford OX1 2BT

rachelpark0410@gmail.com

Abstract. Alzheimer's disease (AD) is one of the most common neurodegenerative diseases in the world, causing dementia among the elderly. Oral microbiome may be associated with AD. This systematic review summarizes the current role of the oral microbiome in the etiology and diagnosis of AD. Articles included were sourced primarily from electronic databases including PubMed, EMBASE, Web of Science, Scopus, and Cochrane Library from January 2011 to August 2022 and in OpenGrey and Google Scholar for grey literature. Relevant studies were selected using a two-stage approach involving the screening of titles and abstracts and full-text evaluation by two authors. Risk of bias was also performed using the Newcastle Ottawa scale (NOS) before qualitative synthesis. 18 studies out of 1079 citations were included in this review. The median NOS rating (IQR) of the reviewed studies was 8 (7.25 – 9). Most studies suggested that there was an association between oral microbiome and AD. Some claimed that oral microbiome might be the risk factor of AD using disparate approaches. Others also detected antibodies to oral microorganisms among AD patients and observed a significantly different alpha diversity among patients with AD than controls. Although limited by the number of studies, this review found that a change in the oral microbiome may be indicative of AD severity. Oral microbiome may be associated with Alzheimer's disease. Some microbial species may be risk factors or aid diagnosis for AD, however more research is still needed to establish their role in AD etiology and noninvasive diagnosis.

Keywords: Alzheimer'S Disease, Oral Microbiome.

1. Introduction

Alzheimer's disease (AD) is a progressive brain disorder characterized by abnormal protein deposits within and around brain cells, causing cognitive problems [1]. AD affects about 57.4 million people with dementia worldwide and it is estimated that the number will rise to 152.8 million by 2050 [2]. As the most common cause of dementia, it is characterized by the disability of remembering, thinking, and making decisions [3]. Patients with AD experience memory loss, a challenge in making judgments and finishing tasks as well as confusion with time and place [3]. With time, the disease progresses and negatively impacts the patient's quality of life. Also, the disease can result in several behavioral complications such as disruptive vocalization, wandering, and aggressiveness [4].

Currently, the etiology of Alzheimer's disease is unknown; however, there are several associated factors with the condition. These include aging, diabetes mellitus, cardiovascular factors, and metal exposure [5-7]. Different theories have sought to explain the pathogenesis of AD but none has gained

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universal acceptance so far [5]. While some authors suggested that Aluminum is neurotoxic and disrupts the balance of pro-inflammatory cytokines within the human primary brain [8, 9], others did not observe a proportionate increase in amyloid-β following increased Aluminum injection in both mice and rabbit models [10, 11]. Moreover, conflicting results have been observed from clinical and epidemiological studies on hypertension and cardiovascular diseases being risk factors for Alzheimer's disease [12-14].

The diagnosis of AD involves the use of imaging techniques such as Magnetic Resonance Imaging (MRI), Computed Topography (CT), and Positron Emission Tomography (PET) as well as cognitive assessment tests such as Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Neuropsychiatric Inventory Questionnaire (NPI-Q) [15, 16]. Though the techniques for diagnosing Alzheimer's disease are satisfactory, some drawbacks that warrant improvement still exist. For example, repeated neuroimaging may be required in some cases which may not be feasible or safe due to increased radiation exposure [17, 18]. Likewise, cognitive and memory tests are subjective with issues concerning their reproducibility [19].

Exploring biomarkers as a tool for the diagnosis of Alzheimer's disease has been the focus of recent research. Though many biomarkers showed a relatively strong association with the disease, none of them have achieved high sensitivity and specificity for AD diagnosis upon external validation [20, 21]. For example, amyloid-β is one of the earliest biomarkers for AD, and the technique of purifying plaques and tangles is relatively mature [20], but patients with other cognitive brain diseases were found to have a similar pattern of biomarker expression [22], making the diagnosis AD more difficult.

With the discovery of periodontal pathogens such as Porphyromonas gingivalis in the postmortem brain of patients with AD [23], the role of the oral microbiome in the pathophysiology of the condition has been the focus of recent research. Some studies suggest that there is an association between the oral microbiome and AD and that the former may serve as a risk factor for the disease [24-26]. However, many of these findings and their summaries have involved mostly preclinical studies [27-30]. Furthermore, saliva and gingival crevicular fluid are reliable biofluids that have been sampled for oral microbiome analysis to suggest stable biomarkers in AD patients [31-33]. However, further comprehensive implementation research may be required before their clinical application.

Currently, little information is available from the synthesis of clinical studies about the relationship and potential utility of the oral microbiome in AD. If available, the study can provide information on the status of research, highlight the clinical usefulness, and identify potential gaps for future studies on the oral microbiome in AD. Therefore, this systematic review summarizes the role of the oral microbiome in the etiology, diagnosis, and monitoring of Alzheimer's disease from current literature.

2. Methodology

This systematic review to highlight the role of the oral microbiome in Alzheimer's disease was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [34] and the review protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID no: CRD42022353517).

2.1. Eligibility Criteria

2.1.1. Inclusion. Original retrospective and prospective clinical studies investigating the oral microbiome in patients with AD were deemed pertinent to this review. In detail, the inclusion criteria set according to the PECOS framework were as follows:

(i)Population: Patients with Alzheimer's Disease as defined by recognized diagnostic criteria (that were reported in the studies) and adults without Alzheimer's disease. Controls included healthy individuals, patients with mild cognitive impairment (MCI), and those with other systemic conditions.

(ii)Exposure: Any taxon of oral microorganisms characterized in biofluids such as saliva and gingival crevicular fluid as well as biofilms like supragingival and subgingival plaque using molecular biology techniques. Also, studies involving other biofluids like plasma and CSF as well as brain tissue that were

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conducted to target microbes chiefly found in the oral cavity such as Porphyromonas gingivalis or Herpes simplex virus 1 (HSV-1) were included.

(iii)Comparator: Diagnostic tests and criteria for AD.

(iv)Outcomes: Ground truth information from imaging, CSF biomarkers, or cognitive assessment tests on Alzheimer's disease status.

(v)Setting: Any setting used in the studies was adopted.

2.1.2. Exclusion. Studies were excluded if they:

(i) included adolescents as control participants (ii) involved animals or were in-vitro studies (iii) were studies that used extraoral samples but did not perform targeted analyses involving an oral microbe. An example was the study conducted by Emery et al (35) (iv) were existing reviews, case reports, case series, letters to the editor, short communications, and commentaries (v) lacked full texts for extracting pertinent data (vi) were not written in English or Chinese.

2.2. Information Sources and Search Strategy

Relevant articles were sourced primarily from electronic databases including PubMed, EMBASE, Web of Science, Scopus, and Cochrane Library from January 2011 to August 2022. Additional searches in OpenGrey and Google Scholar were also done to identify grey literature relating to the review objectives. The search keywords included variables related to the research questions in various combinations based on the PECOS elements. The detailed keywords and search term combinations used in each database are presented in Table 1. Returned citations were exported to EndNote 20 citation manager (Clarivate Analytics, PA, USA) for the removal of duplications after which the authors manually assessed the uniqueness of each citation. Also, manual hand-searching of the bibliography of eligible studies in this review was conducted to complement electronic database searching.

Table 1. Search terms used to identify relevant studies.

Database	Search terms
PubMed	(oral microbiota OR oral microorganism OR oral microbiome OR oral bacteria OR oral fungi OR oral biofilms OR oral microflora OR oral bacterial communities) AND (Alzheimer's disease OR Alzheimer dementia OR Alzheimer syndrome)
EMBASE	Oral microbiota AND Alzheimer's disease; Oral microbiome AND Alzheimer's disease; Oral microorganism AND Alzheimer's disease; Oral bacteria AND Alzheimer's disease; Oral fungi AND Alzheimer's disease; Oral biofilms AND Alzheimer's disease; Oral microflora AND Alzheimer's disease; Oral bacterial communities AND Alzheimer's disease
Scopus	Oral microbiota AND Alzheimer's disease; Oral microbiome AND Alzheimer's disease; Oral microorganism AND Alzheimer's disease; Oral bacteria AND Alzheimer's disease; Oral fungi AND Alzheimer's disease; Oral biofilms AND Alzheimer's disease; Oral microflora AND Alzheimer's disease; Oral bacterial communities AND Alzheimer's disease
Web of Science	(oral microbiota OR oral microorganism OR oral microbiome OR oral bacteria OR oral fungi OR oral biofilms OR oral microflora OR oral bacterial communities) AND (Alzheimer's disease OR Alzheimer dementia OR Alzheimer syndrome)

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2.3. Study selection

This study performed a two-phase assessment of citations to select final articles. First, the title and abstract of the citations were screened for their relevance to investigations on the oral microbiome and AD. Afterward, full-length texts of studies retained from screening were evaluated for the fulfillment of the eligibility criteria. Both study selection phases were performed by two authors independently (PQJ and JA) and disagreements in their choices were resolved by consensus between them following discussions. Concordance between the two reviewers was the basis for the final study selection in this review.

2.4. Risk of Bias (RoB) and Study Quality assessment

Quality evaluation of included observational studies was performed using the Newcastle Ottawa scale (NOS). This tool has three domains that were used to assess the RoB based on the Selection, Comparability, and Outcome/Exposure in the individual studies. All domains were retained in this study for quality assessment and the signaling questions recommended in each domain were used for scoring. An increment score of 1 was added per each signaling question fulfilled by the studies and a sum of the scores accrued from the three domains of the NOS were used to calculate an overall score. RoB ratings were performed independently by two authors (PQJ and JA) and the disagreements were resolved by consensus following discussions.

2.5. Data Collection and Items

Data were abstracted from included studies using a pre-designed electronic spreadsheet (Microsoft Excel for Mac v 16.68). Two independent reviewers performed data collection and referenced the full texts to reach a consensus when there were disparities in entered data. Data items obtained included authors, year, study location, study design, matching controls, time of sampling (prospective vs retrospective), total sample size, sample size for AD patients, sample size for controls, type of controls, diagnostic method for AD and cognition assessment, disease severity, study focus, specific study outcome, sample for oral microbiome analysis, microbiome of interest or isolated, analytical techniques, main results, and study conclusions.

2.6. Result synthesis

Due to the heterogeneity in the objectives of this study and the findings of the included articles, no meta-analysis was performed. Results synthesis was done qualitatively using texts, tables, and figures. Percentages and summary data were presented as reported in the studies and no extrapolation was made by the reviewers.

3. Results

3.1. Study selection

A total of 1079 citations were retrieved from the electronic databases. Following removal of duplicates, 431 citations were screened using their titles and abstracts. After screening, 43 citations were left, and the full-length articles of these studies were obtained and assessed using the eligibility criteria. Furthermore, 25 studies were excluded after full text assessment, and 18 articles were included in this review. The detailed search strategy and study selection process are shown in Figure 1.

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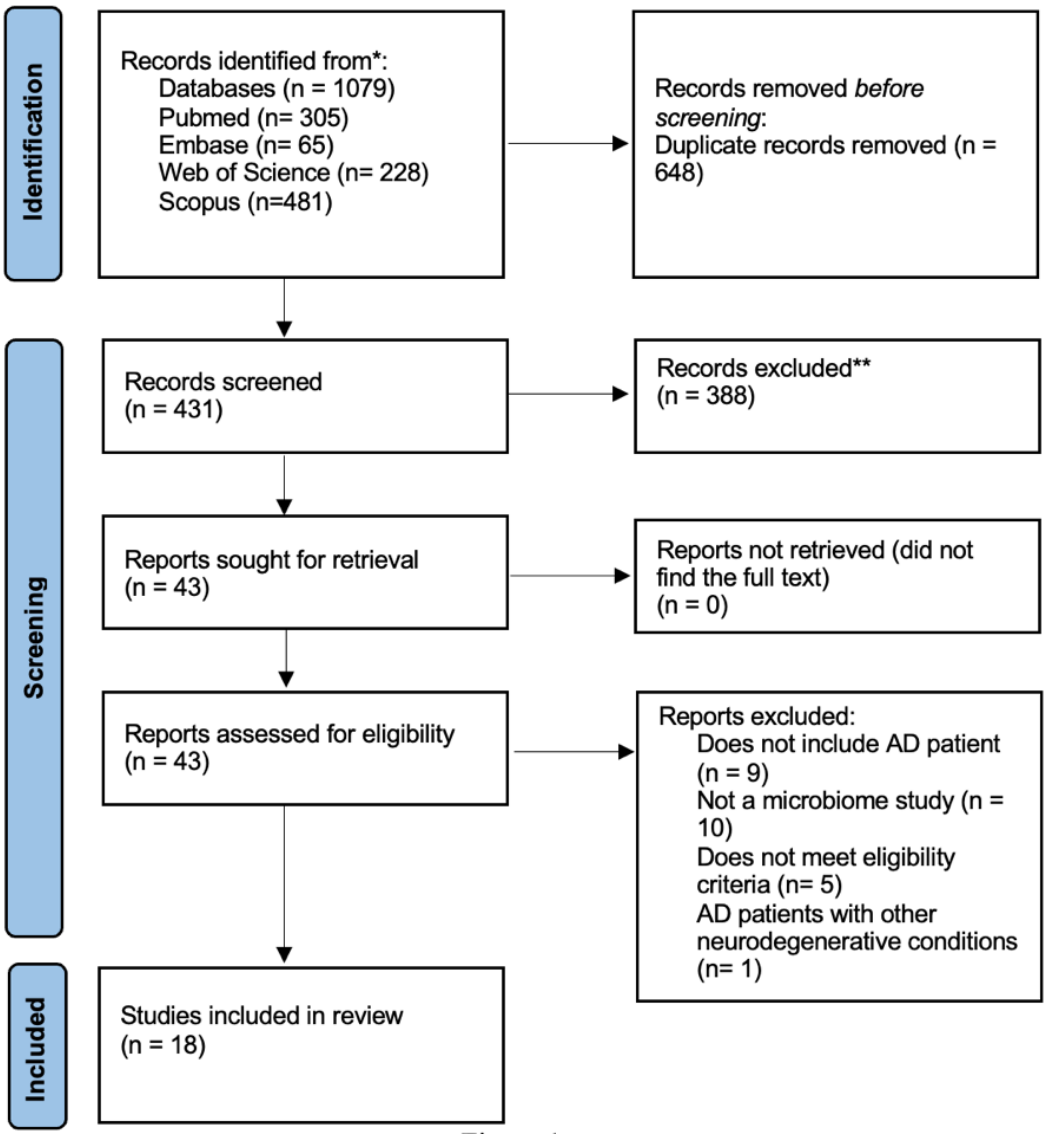

Figure 1. PRISMA flowchart showing the search strategy and study selection conducted in this review.

3.2. Risk of bias assessment

The scores of the NOS ranged from 6 to 9 for the 18 studies included in this review. The median quality rating score (IQR) was 8 (7.25 – 9). Five out of 18 studies had lower scores (6 and 7) while seven studies had score of 8. The detailed scores attained in each domain for the individual studies are presented in Table 2.

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Table 2. Risk of bias assessment of the review studies using the Newcastle-Ottawa Scale.

Author (Year)	Selection	Comparability	Outcome/Exposure	Total
Aragon et al (2018)	4	1	3	8
Bathini et al (2020)	4	2	3	9
Cirstea et al (2022)	4	2	3	9
Fu et al (2022)	4	2	3	9
Guo et al (2021)	4	1	3	8
Holmer et al (2021)	4	2	3	9
Ide et al (2016)	4	1	3	8
Kobayashi et al (2013)	3	2	3	8
Laugisch et al (2018)	3	1	3	7
Leblhuber et al (2020)	4	1	3	8
Liu et al (2019)	3	2	3	8
Moghadam et al (2022)	3	1	3	7
Noble et al (2014)	4	2	3	9
Poole et al (2013)	2	1	3	6
Sansores-Espana et al (2022)	3	1	3	7
Stein et al (2012)	4	1	3	8
Wu et al (2021)	3	1	3	7
Yang et al (2022)	4	2	3	9

3.3. Study characteristics

All studies were published between 2012 to 2022. More reports included were published in 2022 than in any other year with 5 out of 18 studies [36-40]. Most studies emanated from China which was the study location of 3 studies [39, 41, 42], followed by the UK [29, 43], the USA [44, 45], and Taiwan [36, 46] all with 2 studies each.

All studies were observational studies with three main types of study designs. In addition to the 15 case-control studies, there were also 2 cohort studies [43, 44] and 1 cross-sectional study [47]. Also, 3 studies were retrospective studies [29, 45, 48], 1 study used both prospective and retrospective patients [40] while other studies were prospective in nature.

The total sample size in the included studies ranged from 20 to 219 participants with an average of 84 participants. Participants comprised patients with Alzheimer's disease and controls. Six of the studies had the same number of participants for patients with AD and controls [29, 36, 37, 41, 42, 49]. Healthy control was the most common type of control participants which was included in a total of nine studies [29, 36, 37, 40-42, 44, 46, 50]. Likewise, healthy controls and diseased controls (such as those with mild cognitive impairment or severe cognitive decline) were included in five studies [38, 45, 48, 51, 52]. Only two studies included diseased controls only [39, 49] and another two studies employed no controls at all in their report [43, 47].

Within each study, there was either no matching introduced between cases and controls [37, 38, 41, 45, 46, 49, 50]or study groups were matched based on their ages [29, 36, 39, 40, 42, 48, 51, 52] with this representing the most common matching considered by the included studies. There were also other matching factors like sex [36, 39, 40, 48], education [39, 51], and BMI [39, 51]. Three studies did not mention the use of matching controls in their study [43, 44, 47].

Many studies employed the Mini-mental state examination (MMSE) for the cognitive assessment of Alzheimer's disease [36-38, 41-45, 47-49, 51, 52] but only two of them used MRI to detect the brain pattern of the participants [37, 47]. Most studies included patients with mild, moderate, and severe Alzheimer's disease [38, 39, 41-43, 45-52] while others either focused on only one level of AD severity or did not mention the disease severity at all.

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3.4. Qualitative synthesis

3.4.1. Role of the Oral microbiome in the etiopathogenesis of AD. Oral microbiome as an associated factor of Alzheimer's Disease.

Generally, seven studies described the association between the oral microbiome and AD [36, 39-41, 46, 48]. Most of the studies suggested that the oral microbiome is an associated factor of AD [36, 39, 41, 46, 48]. Only one study suggested that there were no significant differences in the composition, diversity, and richness of oral microbiome between AD patients and controls [40]. Furthermore, this study implied that the differences in oral health conditions may be explained by poor oral health practices among patients with A, which is plausible since the cognition of patients with AD decreases significantly and they may not be able to maintain good oral hygiene or attend routine dental visits. What's more, one of the seven studies did conclude that patients with AD had worse oral health and mucosal conditions in comparison to controls [50].

Other included studies (n = 8) described the potential role of the oral microbiome as a risk factor for AD while focusing on three main methods [29, 37, 38, 42, 44, 45, 49, 52]. First, four studies focused on oral microorganisms and their products [29, 37, 38, 42]. One study of these studies used lipopolysaccharide (LPS), the important component of the cell membrane of gram-negative bacteria, of Porphyromonas gingivalis as a surrogate for the presence of the bacteria [29]. Nonetheless, all studies suggested that there were specific types of periodontal pathogenic bacteria in saliva that were significant in AD patients making them potential risk factors for the disease. Second, another four studies investigated the immune response to oral bacteria [44, 45, 49, 52]. Most of the studies detected antibodies to periodontal pathogens [44, 45, 49] while one study detected antibodies to herpes simplex virus 1 (HSV-1) [52]. Among those four studies, only one of them suggests that there were no differences between AD patients and patients with other neurological diseases based on the expression of the antibodies [49].

Sampling and molecular techniques for oral microbiome analysis in AD patients

Most of the biological samples used in the included studies were saliva and blood. Among the five studies that employed blood samples, three studies used serum [43-45], and the other two used plasma [49, 52]. Among the rest of the studies, five used saliva [36, 39, 42, 50, 51], and others used intraoral samples such as subgingival plaque [38], subgingival biofilm [48], oral biofilm [46], oral swabs [37, 40], and gingival crevicular fluid (GCF) [38, 41, 47]. Also, three studies were performed using brain tissues or cerebrospinal fluid (CSF) [29, 49].

Disparate molecular techniques were employed in the included studies to identify the type of microbes, bacteria richness, and the antibodies to these microorganisms. The most common technique was 16S rRNA sequencing. Eight out of 18 studies used this method [36, 39-42, 46, 48, 51] to identify and compare the bacterial diversity in the oral environment. Three studies employed quantitative polymerase chain reaction (qPCR) [37, 38, 49], focusing on the quantitative measurement of bacteria. Rogosa agar and blue mitis-salivarius agar with bacitracin were used to culture bacteria in one study [50].

Regarding the evaluation of antibodies to pathogens, enzyme-linked immunosorbent assay (ELISA) was frequently used to detect antibodies in the blood as it was used in four included studies [39, 43, 45, 52]. Immunoblotting was also used in two studies to identify targeted proteins through the interaction with antibodies [29, 44].

3.4.2. Prevalent microbes in the oral cavity of patients with AD compared to those without AD. In general, more studies observed a significantly different alpha diversity among patients with AD than controls. For individual study results, three studies suggested that there was a lower alpha diversity in AD patients [39, 42, 46], while there were two studies that observed that alpha diversity was higher among AD patients [40, 48]. One study found a 90% overlap in alpha diversity and a 5-6% difference in beta diversity between AD patients and controls [36]. This was also supported by another study that observed considerable overlap in the beta diversity [41], suggesting that there was no difference in beta

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diversity between AD patients and controls. There were more bacteria species with increased abundance in AD patients than controls compared to the species with decreased abundance (Table 3). This provided a wide range of species that positively correlated with increased alpha diversity in AD patients.

Table 3. Difference in the oral microbiome of AD patients compared to controls.

Decreased abundance	Increased abundance
Rothia (36, 40, 42, 48) *Streptococcaceae (36, 40, 41, 46)* *Actinomycetaceae (40, 42, 48)* *Cardiobacterium (41, 46)* *Porphyromonadaceae (39, 46)* *Fusobacterium (45, 46)* *Aggregatibacter aphrolius (41)* *Haemophilus parainfluenzae (41)* *Haemophilus haemolyticus (41)* *Actinobacillus (42)* *Alloprevotella (46)* *Prevotella (39)* *Firmicutes (40)*	*Lactobacillales (41, 46)* *Fusobacterium nucleatum (37, 45)* *Capnocytophaga (36, 41)* *Prevotella (37, 41)* *Weeksellaceae (40)* *Porphyromas gingivalis (36)* *Eubacterium (36)* *Selenomonas (36)* *Veillonella parvula (41)* *Bifidobacterium dentium (41)* *Atopobium parvulum (41)* *Slackia exigua (48)* *Lachnospiraceae bacterium (48)* *Moraxella (42)* *Leptotrichia (42)* *Sphaerochaeta (42)* *Shuttleworthia (46)* *Bacilli (46)* *Firmicutes (46)*

3.4.3. Synchronous/metachronous oral microbiome-related diseases in patients with AD. Periodontitis.

The study carried out by Fu et al suggested that periodontal infection and related oral microbiome are associated with AD [36], which is supported by other studies suggesting the relationship between cognitive impairment and severity of periodontitis [53-56]. In this study, the anti-Porphyromonas gingivalis lipopolysaccharide (LPS) antibody was found to be elevated in AD patients compared to healthy controls, indicating the possible increase of Porphyromonas gingivalis among AD patients.

Stein et al also made a similar conclusion that periodontal diseases and periodontal pathogens may be risk factors for AD onset or progression [45]. Specifically, antibodies to Prevotella intermedia increased in AD patients both at baseline and after conversion. This was supported by Moghadam et al, who also found an increased abundance of Prevotella intermedia among AD patients [37]. But Lehlhuber et al observed that Prevotella intermedia was not significant for the onset and development of AD and that species like Treponema denticola, Treponema forsythia, and Porphyromonas gingivalis were associated with the disease [47]. But the study concluded that more reports were needed to confirm their findings.

Dental caries

Lactobacillus was found to be enriched in AD patients in the studies carried out by Wu et al and Guo et al [41, 46]. The conclusion made by Aragon et al, which is that AD patients had worse oral health and had more dental diseases including dental caries [50], also supported this result since Lactobacillus is implicated in the development of dental caries. Similar to Lactobacillus, Streptococcus mutans was found to increase in AD patients indicating that they have a higher risk of developing caries in the study by Aragon et al [50]. Moghadam et al suggested that even though there were relatively more Streptococcus mutans in AD patients, the result was not statistically significant [37], while Cirstea et al suggested that Streptococcaceae was less abundant in AD patients [40], which was also supported by Fu et al [36].

Cold sores

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The study carried out by Kobayashi et al was the only study focusing on the association between HSV 1 and AD [52]. HSV-1 is the most common virus that causes cold sores which are small blisters on the lips [52]. The result showed that there was no significant difference in anti-HSV antibodies between AD patients and controls.

3.4.4. Role of the Oral microbiome in the diagnosis of AD. The presence or absence and the change of the abundance of certain bacteria might assist the future diagnosis of AD, for example, Porphyromonas gingivalis and Lactobacillus, but more research is needed to test their accuracy in the diagnosis. The research by Bathini et al aimed to predict patients with AD by using saliva sampling. It suggested that specific bacteria isolated in AD had a sensitivity of 0.63 to 0.65 and a specificity of 0.53 to 0.56 and the linear discriminant analysis applied to oral bacteria had an accuracy of 0.94 [51]. The oral microbiome may be relatively reliable to assist the diagnosis of AD, but sensitivity, specificity, and accuracy need to be verified and improved in a large prospective study before consideration in the clinical diagnosis of AD.

3.4.5. Oral microbiome as an indicator of cognitive decline in patients with AD. Two studies focused on the association between the oral microbiome and AD severity. The study carried out by Leblhuber et al suggested that some bacteria may be an indicator of cognitive decline in AD, for example, AD patients with Porphyromonas gingivalis had lower scores on Mini-Mental State Examination (MMSE) [47]. But this finding is still preliminary, and more research is needed to test the reliability of this result [47]. Another study came up with the conclusion that after six months, poor oral health, for example, the presence of periodontitis, correlated with a marked decline in the cognitive ability of patients with AD [43]. But only a few participants were included in this study which may need to be confirmed in future studies. However, the result did support the previous conclusion by Leblhuber et al due to the similar pattern between the degree of oral infection and severity of AD.

4. Discussion

Alzheimer's disease (AD) is the most common cause of dementia and affects many people. This systematic review found that the oral microbiome may be associated with AD and may be a risk factor for the disease. Even though more research is needed to identify specific species of microorganisms that may be implicated, this review affirms that there is a potential to develop noninvasive tests using saliva and other intraoral samples to target the oral microbiome for preliminary identification of patients with AD.

Many reviewed studies suggested that the oral microbiome might be associated with AD. Periodontitis was found to be the immune response of microbial overgrowth in subgingival tissue [57], influencing the composition of the oral microbiome, while AD is also associated with inflammation. Most of the related studies had high quality with a score of 8-9 in NOS so the result has a low risk of bias. Also, the association between AD and oral microbiome is supported by other reviews [58-60] and provides a possible pathway for the oral microbiome to be further involved in the mechanism, diagnosis, and treatment of AD. However, there is still a possibility that there may be an effect modifier influencing the association between the oral microbiome and AD (such as age) which needs to be unraveled. Also, the specific mechanism to explain this association is not clear. Future studies focusing on these areas are needed in the future.

Some of the reviewed studies also indicated that the oral microbiome is a possible risk factor for AD. Interestingly, three studies with the conclusion that oral bacteria may be the risk factor of AD had a score of 8-9 in NOS, but the study with the negative result had a NOS rating of 7, which may support the finding of OM as a risk factor of AD. This finding can be explained by the fact that the deteriorating oral inflammation can develop into a severe systemic immune response and disrupt the normal functioning of removing damaged or misstructured neuroproteins in the brain, providing a toxic environment for the accumulation of amyloid beta plaques, gradually developing neurodegeneration and causing Alzheimer's disease [24-26, 61]. Also, almost all reviewed studies suggested that there were

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specific types of periodontal pathogenic bacteria in saliva that were significant in AD patients making them potential risk factors for the disease. While most studies suggested that various species of the oral microbiome have 'Increased abundance' in AD patients, there are specific species that are reduced in AD patients such as Rothia and Streptococcaceae compared to non-AD patients. This adds more evidence for the oral microbial factors related to Alzheimer's disease etiology and assists the diagnosis of AD using antibodies of specific oral bacteria.

According to the selected studies, oral microbiome might assist in the diagnosis of Alzheimer's disease, but more research is needed to improve the reliability of this finding. Even though there is a significant difference in the diversity, density, and amount of oral microbiome between AD patients and non-AD patients [24, 62, 63], the specific type of microorganism that cause the difference varied between different selected research. Currently, certain saliva biomarkers and other oral tests for bacteria can only assist AD diagnosis with brain images and mental testing [64, 65]. More specific research is needed to have clear criteria for the diagnosis of AD based on oral microorganisms in the future.

Although this review is unique in its summary of clinical microbiome studies, there are some limitations. Firstly, most of the studies selected focused on the association between oral microbiome and AD while only a few studies focused on the diagnosis role of oral microbiome, indicating that the role of oral microorganisms in the diagnosis of AD has not been fully elucidated. Future studies should focus on operationalizing the oral microbiome as a possible diagnostic tool for AD since there may be an association between the oral microbiome and AD. Secondly, the majority of studies focused on the oral bacteriome rather than viruses, fungi, and other possible microorganisms. Research on disparate constituents of oral microorganisms is needed for a thorough understanding of the role of oral microbiome in AD. Thirdly, only the articles written in English and Chinese were considered in this review which excluded some pertinent studies that may have been written in other languages. Finally, there were many molecular techniques and sampling methods used in the different studies which may introduce heterogeneity in the study synthesis. More control over the type of sampling and molecular techniques used for oral microbiome analysis will lead to a more accurate and reliable analysis in the future.

5. Conclusions

In conclusion, this systematic review found that the oral microbiome may be associated with Alzheimer's disease and may even be a potential risk factor for the disease. However, it is unclear whether this association has etiologic implications or whether these changes in the oral microbiome may be due to associated worsening oral health status among patients with AD. In this regard, more research is needed to elucidate the exact mechanisms or direction of the association between the oral microbiome and AD. Additionally, the changes in the oral microbiome may also be indicative of an increased cognitive decline among patients with AD. Albeit, this is only from limited sources in this review and further research is also required to bolster this finding. Overall, this review showcases the potential to develop noninvasive tests based on intraoral samples and the oral microbiome for early/preliminary identification of AD and monitoring of cognitive decline among patients with AD.

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