ABSTRACT

Several studies indicate a possible association between periodontitis and dementia. Additionally, the available scientific literature also suggests that periodontitis may be related to cognitive impairment. This review aimed to systematically assess and evaluate the scientific literature on the impact of periodontitis on the risk of dementia and cognitive impairment.

The online scientific databases (PubMed and Scopus) were searched for original English language, longitudinal studies that assessed the role of periodontitis in determining the risk of dementia and cognitive impairment. In total 10 studies complied with the inclusion criteria, with 5 concerning dementia as the outcome and 5 cognitive impairment. The studies included in this review were also assessed for the quality of evidence in four major and one minor domain. Four studies reported association between periodontitis and dementia. Evidence supporting the possible role of periodontitis in elevating the risk of dementia was of low to moderate quality. In the case of cognitive impairment, although there seemed to be higher likelihood of cognitive impairment with poor periodontal status, results were less straightforward. All five studies with cognitive impairment as the outcome were of low quality.

This review suggests that periodontitis is likely to increase the risk of dementia. However, the amount and quality of evidence currently available is insufficient and of moderate to low quality to draw any firm conclusions. Further studies with better study designs, longer study duration and more comprehensive assessment of periodontitis and cognitive status are needed to elucidate the association of periodontal health with cognition and dementia.
ABBREVIATIONS

Aβ: Amyloid beta
ABL: Alveolar bone loss/loss of alveolar bone
AD: Alzheimer’s disease
APOE: Apolipoprotein E
APP: Amyloid precursor protein
ARIC: The atherosclerosis risk in communities study
BBB: Blood brain barrier
BOP: Bleeding on probing
CAL: Clinical attachment loss/loss of clinical attachment
CPI: Community periodontal index
CPITN: Community periodontal index for treatment needs
CRP: Serum C-reactive protein
CSF: Cerebrospinal fluid
CVDs: Cardiovascular diseases
DLB: Dementia with Lewy bodies
DMFT: Decayed, missing, and filled teeth index
DSM: Diagnostic and statistical manual of mental disorders
DSS: Digit symbol substitution
DWR: Delayed word recall
FINGER: Finnish geriatric intervention study to prevent cognitive impairment and disability
GBI: Gingival bleeding index
GCF: Gingival crevicular fluid
GDS: Geriatric depression scale
HEPESE: Hispanic established populations for epidemiologic studies of the elderly
ICD: International statistical classification of diseases and related health problems
IL-6: Interleukin-6
LHID: Longitudinal health insurance database
LPS: Lipopolysaccharide
MAPT: Multi-domain Alzheimer preventive trial
MCI: Mild cognitive impairment or Cognitive impairment
MMI: Mild memory impairment
MMSE: Mini mental state examination
MRI: Magnetic resonance imaging
NHI: National health insurance - Taiwan
NHIRD: National health insurance research database of Taiwan
NSAIDs: Non-steroidal anti-inflammatory drugs
PAQUIDENT: Paquid dental study - France
PCI: Plaque control index
PDI: Periodontal disease index
PPDs: Periodontal pocket depths
PreDIVA: Prevention of dementia by intensive vascular care
PSP: Progressive supra-nuclear palsy
ROS: Reactive oxygen species
TBI: Traumatic brain injury
TNF-α: Tumor necrosis factor alpha
VaD: Vascular dementia
VCI: Vascular cognitive impairment
WF: Word fluency test.
WHO: World health organization
WMS-R: Wechsler memory scale – revised
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1 INTRODUCTION

Periodontitis is the inflammation of tooth supporting tissues. In severe cases, deterioration of periodontal tissues culminates into tooth loss (Silva et al. 2017). Chronic periodontitis is the most common form of periodontitis affecting about one third of world population (Branco et al. 2015). It arises as an inflammatory response mounted against sub-gingival plaque bacteria. Although it is primarily an infectious pathology, dysregulated or hyperactive immune response plays a crucial role in its development and progression (Suresh et al. 2017). The impact of periodontitis spreads beyond oral health and is proposed to affect systemic health. It is regarded as an important determinant for systemic conditions like diabetes, cardiovascular diseases and adverse pregnancy outcomes (Pitiphat et al. 2008, Macedo Paizan & Vilela-Martin 2014, Lönn J et al. 2018).

Dementia is a syndrome characterized by progressive deterioration of cognitive function and functional incapacitation. It is mainly prevalent in elderly individuals, with 5-7% of 60 years or older individuals affected by it worldwide (LoGiudice & Watson 2014). Age and genetic predisposition are the major risk factors for dementia (Kalantarian et al 2013). Furthermore, number of lifestyle and environmental factors are proposed to be important determinants of dementia (Ylilauri et al. 2017). Dementia is caused by a number of pathologies, with Alzheimer’s disease (AD) being the most common cause, followed by vascular cognitive impairment (VCI) and dementia with Lewy bodies (DLB) (Tzeng et al. 2016).

Dementia pathology (mainly AD) may occur years before the first symptoms appear. Studies have highlighted the role of periodontitis in the progression of dementia and cognitive deterioration (Dintica et al. 2018, Gusman et al. 2018). However, more research is needed to establish its role as a risk factor for dementia. A few studies have indicated that periodontitis increases the risk of dementia and cognitive decline (Oh et al. 2018). Multiple mechanisms have been proposed, such as the inflammatory model (Gallart-Palau et al. 2017). Tooth loss, a direct consequence of periodontitis, also independently increases the risk of dementia and cognitive impairment (Nilsson et al. 2013).

With a significant rise in elderly population, prevalence of dementia alone is projected to surpass 100 million by 2050 (Koch & Jensen 2016). It is hence important to identify risk factors which can contribute towards understanding the multifactorial etiology of the disease. In view of these notions,
the role of periodontitis as a modifiable risk factor for dementia and cognitive impairment needs to be investigated.

2 LITERATURE REVIEW

2.1 PERIODONTITIS

2.1.1 Definition
Periodontitis is the inflammation of tooth supporting tissues that results in deterioration of periodontal ligament and resorption of alveolar bone. It is characterized by gingival inflammation, formation of periodontal pockets, clinical attachment loss and resorption of alveolar bone. Periodontal pockets form as the widening of gingival sulcus due to gingival inflammation. Whereas clinical attachment loss (CAL) is the term describing the apical migration of junctional epithelium, that forms the base of the healthy gingival sulcus. As the inflammation spreads to the alveolar bone it causes its resorption that may eventually culminate into tooth loss (Newnan et al. 2012).

Chronic periodontitis is the most common form of periodontitis that arises in response to sub gingival plaque bacteria (Armitage 1999). Several plaque bacteria, predominantly gram-negative species such as Porphyromonas gingivalis are associated with periodontitis (Hajishengallis 2012). Although periodontitis is triggered by plaque bacteria, host immune response prompted against bacterial stimulus plays a predominant role in determining the extent and severity of periodontal tissue breakdown (Kinane & Marshall 2001).

Several factors such as poor oral hygiene, diabetes, medication and smoking significantly increases the risk of periodontitis. Periodontitis is a slowly progressing chronic pathology, however, in the presence of multiple predisposing factors, periodontal tissue breakdown undergoes frequent acute exacerbations (Genco & Borgnakke 2013).

The clinical consequences of periodontitis spreads beyond its effects on oral cavity. In addition to causing difficulty in mastication and speech, periodontitis adversely affects psychosocial wellbeing and overall quality of life. Furthermore, it is suggested to be a risk factor for multiple systemic diseases
such as diabetes, cardiovascular diseases and adverse pregnancy outcomes (Gross et al. 2017). Chronic periodontitis serves as a constant trigger for the expression of inflammatory mediators and is proposed to increase the risk of many systemic diseases such as cardiovascular diseases (CVDs) and diabetes. Furthermore, increasing evidence also suggest that periodontitis facilitate in the development of neurodegenerative disorders such as dementia (Kamer et al. 2012, Kamer et al. 2015, Nilsson et al. 2017).

2.1.2 Prevalence
Periodontitis is the 6th most common chronic disease affecting about one third of world’s population. It is mostly prevalent in adults (35 years or older) but is also observed in younger individuals (Silva et al. 2017). The prevalence of periodontitis has been reported to lie between 20-50% worldwide, however most estimates are believed to underestimate the absolute numbers, with prevalence among the middle-aged individuals (35-44 years old) alone estimated to be between 15-20% globally (WHO 2012). About 10-15% of world’s population is affected by severe periodontitis that often culminates into tooth loss if left untreated (Ballini et al. 2015).

The prevalence of periodontitis increases with age. Severe periodontitis, in particular, is relatively more prevalent among elderly individuals. Age-related factors such as increased prevalence of systemic diseases, decreased effectiveness and frequency of oral health practices and propensity to have general systemic inflammatory state is suggested to contribute to increased susceptibility of periodontitis among the elderly. The prevalence of periodontitis has been on a rise, attributed to increase in population and increased proportion of elderly. Furthermore, people are retaining more teeth well into their old age that could explain for high prevalence of periodontitis (Kassebaum et al. 2017).

2.1.3 Types of Periodontitis

2.1.3.1 General classification of Periodontitis
Periodontitis is mainly classified into aggressive and chronic types, with each type further stratified into localized and generalized subtypes. In addition to aggressive and chronic periodontitis other less common types of periodontal diseases include periodontitis as a manifestation of systemic diseases,
necrotizing periodontal diseases, periodontitis associated with endodontic lesions and periodontal disease as part of developmental or acquired deformity diseases (Armitage 1999).

Chronic periodontitis initiates as the inflammation of gingiva triggered by plaque bacteria, giving rise to gingivitis. If left untreated or uncontained by the immune response mounted to deal with the bacterial challenge, gingival inflammation spreads to periodontal ligament and alveolar bone resulting in progression of gingivitis into periodontitis (Armitage 1999).

2.1.3.2 Classification of Chronic Periodontitis
Chronic periodontitis is divided into localized and generalized types which demonstrates the extent of dentition affected by periodontal disease. This classification of chronic periodontitis is based on the percentage of sites or teeth that exhibits clinical attachment loss and resorption of alveolar bone. Diagnosis of localized periodontitis is assigned when less than 30% of teeth or sites displays clinical attachment loss and alveolar bone resorption. Whereas general periodontitis indicates the involvement of more than 30% of teeth or sites (Wiebe & Putnins 2000).

2.1.3.3 Mild, Moderate and Severe Periodontitis
Furthermore, periodontitis is also categorized as “mild periodontitis”, “moderate periodontitis” and “severe or advanced periodontitis”, depicting severity of periodontitis. The severity of periodontitis is ascertained by measuring amount of clinical attachment loss. Mild periodontitis presents with 1-2 mm of clinical attachment loss, while moderate periodontitis infers 3-4 mm of attachment loss. Clinical attachment loss of 5 mm or beyond is referred to as severe periodontitis (Wiebe & Putnins 2000).

2.1.4 Pathophysiology of Periodontitis

2.1.4.1 Characteristics of Periodontitis
The classical features of periodontitis comprise of gingival inflammation, periodontal pocket formation, clinical attachment loss and resorption of alveolar bone. Relatively less frequently encountered features include gingival recession and tooth mobility, observed in severe periodontitis. Gingival inflammation incurs a number of changes in the healthy gingiva including gingival swelling, loss of gingival stippling and changes in color and contour of gingiva (Loesche & Grossman 2001).
On the spread of gingival inflammation, gingival sulcus increases in depth, eventually leading to striping away of gingiva from the tooth surface. This marks the formation of periodontal pockets and transition of gingivitis into periodontitis. Degree of periodontal pocket depth may be indicative of severity of periodontal disease. However, such should be implied with caution as it underestimates the disease in case of gingival recession where periodontal pockets remain shallow and overestimates in cases where gingiva is extensively swollen (Loesche & Grossman 2001).

Clinical attachment loss assesses position of junctional epithelium against the tooth and is a measure of extent of apical migration of junctional epithelium. It is a superior indicator of periodontal tissue destruction in comparison to periodontal pocket depth and accounts for gingival changes such as gingival recession or gingival overgrowth (Armitage & Cullinan 2010). Alveolar bone resorption is another classical feature of periodontitis, which in severe cases is clinically manifested as loosening of teeth. It may be clinically assessed during periodontal probing, however in majority of instances radiographic assessment is undertaken for adequately determining the extent and pattern of bone loss (Cochran 2008).

2.1.4.2 Etiology of Periodontitis

Dental Plaque
Periodontitis is an infectious disease caused by pathogenic bacteria in mature dental plaque. The microbial biofilm called ‘dental plaque’ is the tenacious admixture of oral bacteria in a complex extracellular matrix that forms on tooth surface. Hundreds of bacteria have been isolated from dental plaque, majority of which are commensal in nature, having no pathological significance (Paster et al. 2001). However, multiple bacterial species predominantly the gram-negative types such as Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola and Prevotella intermedia are implicated as periodontal pathogens responsible for triggering the host immune response leading to the development and establishment of periodontitis (Socransky et al. 1998). The extracellular component of plaque is mainly derived from saliva and comprises of various organic and inorganic salivary components (Peterson et al. 2014).
Dental plaque is classified as supra-gingival and sub-gingival plaque according to its position relative to gingival margin. Supra-gingival plaque is part of dental plaque lying above the gingival margin whereas part of dental plaque sheltered within gingival sulcus is referred to as sub-gingival plaque. It is the sub-gingival plaque that holds key importance in pathogenesis of periodontitis. The overall composition and pattern of sub-gingival plaque vary little from supra-gingival plaque. However, it is more resolute, achieves maturation at a relatively faster pace and harbors more potent and greater proportion of periodontal pathogens such as spirochetes. The formation and maturation of plaque is driven by inter-microbial interaction, facilitated by presence of local and systemic factors. Furthermore, host immune system is also suggested to play a significant part in establishing and sustaining the dysbiosis that triggers the pathological process leading to periodontitis (Loesche & Grossman 2001).

Formation of plaque starts with the development of a layer of organic matrix called acquired pellicle upon which successively various bacterial species colonize. The aerobic non-pathogenic bacteria are the first to populate followed by virulent gram-negative anaerobic types (Darveau et al. 1997). The host inflammatory response triggered by sub-gingival plaque clinically manifests as gingival inflammation. The gingival inflammation leads to increase in size of gingival sulcus that allows further accumulation of sub-gingival plaque. This subsequently produces an immune response of even larger magnitude leading to progression of gingivitis towards periodontitis (Cekici at al. 2014).

**Host immune response**

The immune response in periodontitis is complex and involves both the innate and acquired segments of immune system. However, there is no clear delineation between the effects of innate and acquired immune system with both working in cooperation and overlapping the effects of each other. Although periodontitis is triggered by plaque bacteria and can essentially be categorized as an infectious disease, it is the host immune response that plays the chief role in the pathological process leading to destruction of periodontal tissues (Wilensky et al. 2015).

This is supported by the finding that poor oral hygiene which is indicative of extensive accumulation of plaque dominated by gram negative bacteria, does not always coincides with the development of periodontitis (Meyle & Chapple 2015). On the other hand, susceptible individuals can develop severe periodontitis even in the presence of plaque scarcely populated by periodontal pathogens, although the
classical periodontal pathogens are demonstrated in such individuals as well. Another important finding advocating the more significant part of host immune system in periodontitis is the fact that although several periodontal pathogens have been linked with periodontitis in general or with specific types of periodontitis. No single pathogen has yet been found to be the sufficient cause of periodontitis (Hajishengallis 2015).

It is proposed that in susceptible individuals, the host immune system is dysregulated that leads to a hyperactive immune response against plaque bacteria. This hyperactive immune response leads to extensive periodontal tissue breakdown, even if the microbial challenge is minimal (Khan et al. 2015). The hallmark features of periodontitis, namely, periodontal pocket formation, clinical attachment loss and resorption of alveolar bone are brought about by cytokines released by immune cells to counteract microbial challenge (Shah et al. 2017). Furthermore, established risk factors for periodontitis such as systemic comorbidities increase the risk of periodontitis by contributing to dysregulation of host immune response (Zhu & Nikolajczyk 2014).

The inflammatory response in periodontitis is initially mounted as a physiological response to contain the bacterial stimulus, which converts into a pathological chronic inflammation if the inflammation fails to clear the constant stream of bacterial stimulation. After the recognition of bacteria or bacterial products by innate immune system, chemokines and cytokines are expressed to recruit phagocytes. Furthermore, the complement system is also triggered to contain the bacterial challenge (Cekici et al. 2014).

As the innate immune system is overwhelmed by the bacterial challenge it causes the activation of acquired segment of immune system, bringing in other types of immune cells to counteract the periodontal infection. The acquired immune system works side by side along with the already functional innate immune system. In majority of the cases, there establishes an equilibrium between constant bacterial stimulus and continuous counteractive immune response leading to establishment of mild or moderate chronic periodontitis. However, in susceptible subjects the immune response is dysregulated that leads to extensive destruction of periodontal tissues, which clinically manifests as severe periodontitis (Cekici et al. 2014).
2.1.4.3 Development and Progression of Periodontitis

Periodontitis develops in a stepwise manner, progressing in severity as the host inflammatory response becomes more potent. Initially only the gingiva is involved, clinically apparent as gingivitis. But as the inflammation spreads it involves periodontal ligament and alveolar bone in pathological process, resulting in eventual loss of clinical attachment and resorption of alveolar bone thus producing periodontitis (Robinson 1995).

The initial lesion of periodontitis develops within 2 to 4 days of plaque accumulation, which is clinically indistinguishable from healthy gingiva. The only discernible changes are at the histological level, brought about by resident leukocytes and endothelial cells. There is migration of neutrophils to the site of inflammation in response to cytokines released by junctional epithelium, accompanied with increased flow of gingival crevicular fluid (GCF). On progression of initial lesion to early lesion, gingival inflammation becomes clinically evident and is accompanied by further increase in GCF flow. Histologically, there is increased proportion of neutrophils at the affected site, along with migration of other types of leukocytes such as macrophages (Cekici et al. 2014).

If the microbial challenge is not cleared and further exacerbation of inflammatory response occurs, early lesion progresses into established lesion, which presents clinically as chronic gingivitis of moderate to severe intensity. At this stage gingival inflammation is well pronounced, with proliferation of epithelium into underlying connective tissue. The cell infiltrate is now predominantly populated by lymphocytes and plasma cells, with junctional epithelium beginning to detach from tooth surface at this point (Cekici et al. 2014).

Any further damage to periodontium marks the formation of advanced lesion and transition of gingivitis into periodontitis. The inflammatory response reaches its peak and leads to apical migration of junctional epithelium clinically manifested as clinical attachment loss. Furthermore, the inflammatory process involves tooth supporting alveolar bone leading to its resorption. The GFC is predominantly concentrated by neutrophils, while underlying connective tissues are populated by plasma cells (Cekici et al. 2014).
2.1.5 Diagnosis of Periodontitis

Diagnosis of periodontitis is based on clinical findings which includes periodontal pocket formation (with or without gingival recession), bleeding on probing (BOP), clinical attachment loss and alveolar bone loss. These clinical findings are calibrated to determine the extent of periodontal damage and are usually supplemented with radiographic assessment which is valuable in determining the extent and severity of periodontitis, as well as in delineating the pattern and extent of alveolar bone loss (Highfield 2009). These measures form the basis of diagnostic criteria highlighted in standard diagnostic manuals such as International Statistical Classification of Diseases and Related Health Problems (ICD) (WHO 2016).

Clinical features are enough to ascertain the presence of periodontitis, but to conclusively highlight a certain case, as of chronic periodontitis, clinical findings are assessed in context of age, presence of sub-gingival plaque, local risk factors and pace of disease progression, along with medical and dental history (Highfield 2009).

A number of indices of periodontal health such as Community Periodontal Index for Treatment Needs (CPITN), Periodontal Disease Index (PDI) and Community Periodontal Index (CPI) among others are used for screening and diagnosing periodontitis both at the clinical and epidemiological level (Beltrán-Aguilar et al. 2012). Although different periodontal indices assess periodontal health based on above mentioned measures of periodontitis. Not all measures are employed by each index and there exists variation in the number and combination of measures used (Buenco et al. 2015). Most of these indices do not only provide estimation of periodontal health but also provide an approximate estimate of treatment that is needed to be administered (Dhingra & Vandana 2011).

One of the most commonly used periodontal index is community periodontal index (CPI) which is a modified version of community periodontal index of treatment needs. CPI assesses the periodontal status through periodontal probing, clinical attachment loss, gingival bleeding and presence of calculus (Table 1). Instead of screening the entire dentition CPI assesses only a limited number of teeth that are found to be representative of entire dentition, thereby delivering a comprehensive assessment of periodontal health in an efficient manner (Dhingra & Vandana 2011).
The severity of periodontitis is defined as per the measurements of PPDs, CAL or alveolar bone loss (ABL). However, none of these measures are accurate indicators and needed to be used in concordance. For instance, PPDs however commonly used, under or overestimates periodontal deterioration based on the state of gingiva (Highfield 2009). Although CAL is considered as the standard measure of periodontal disease, it is more relevant in depicting the history of disease and less reliable in ascertaining the present status of periodontal tissues (Buenco et al. 2015).

The clinical assessment of periodontal tissues is undertaken by means of periodontal probing in which a periodontal probe such as CPITN probe, is inserted into periodontal pockets to measure PPDs and CAL. Although a rough estimate of ABL can also be obtained by periodontal probing, radiographic assessment is almost always obtained. The probe is inserted parallel to vertical axis of tooth under slight force and ran circumferentially to identify points of deepest penetration for each tooth. PPDs are measured as the distance from the floor or bottom of the periodontal pocket to gingival margin, while CAL is measured as the distance from the bottom of the pocket to cemento-enamel junction (Hefti 1997).

<table>
<thead>
<tr>
<th>Category/code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Healthy periodontium</td>
</tr>
<tr>
<td>1</td>
<td>Gingival bleeding on probing</td>
</tr>
<tr>
<td>2</td>
<td>Calculus detected and bleeding on probing</td>
</tr>
<tr>
<td>3</td>
<td>Periodontal pockets lying between 4 - 5 mm / shallow periodontal pockets</td>
</tr>
<tr>
<td>4</td>
<td>Periodontal pockets being 6 mm or more / deep periodontal pockets</td>
</tr>
</tbody>
</table>

2.1.6 Treatment of Periodontitis

Management of periodontitis is based on the principal of establishing plaque control and preventing further deterioration of periodontal tissues (Teughels et al. 2014). The treatment modalities employed to do so are divided into non-surgical and surgical types, which may be supplemented with antimicrobials where needed. In line with the principles of conservative and noninvasive management of diseases, nonsurgical treatment options such as professional debridement of plaque through
techniques such as scaling are first undertaken (Newman et al. 2012). Surgical treatment such as
gingivectomy is reserved for severe cases or undertaken in cases where extent of periodontal damage is
extensive or non-surgical measures have failed (Drisko 2014).

Any active manipulation of periodontium, whether surgical or non-surgical are delivered to remove
plaque and increase the effectiveness of oral hygiene practices undertaken thereafter (Gao et al. 2014).
Regardless of the treatment modality opted for, instituting oral hygiene measures and controlling for
risk factors forms an integral part of treatment plan (Genco & Borgnakke 2013).

2.1.7 Risk factors for Periodontitis
Multiple local, systemic and lifestyle factors increase the risk of periodontitis. Several mechanisms
have been proposed by which various factors individually or synergistically impart elevated risk of
periodontitis. The main pathway by which most of the established risk factors predisposes to
periodontitis is dysregulation of immune response (Jain & Mulay 2014, Hong M et al. 2016).
Furthermore, multiple factors also assist in the development of periodontitis by facilitating maturation n

Majority of the risk factors for periodontitis are modifiable in nature that render periodontitis to
preventive regimens. Furthermore, non-modifiable factors such as age and gender are also suggested to
increase the risk of periodontitis through indirect pathways that can also be explored as targets for
preventive strategies (Genco & Borgnakke 2013, Persson 2017).

2.1.7.1 Non-modifiable factor

Age
The prevalence and severity of periodontitis increases with age. The prevalence of severe periodontitis
is 15% higher among the elderly individuals as compared to general population (Khocht et al. 2010).
This is evident by the association between CAL and increasing age, with increase in CAL being
consistent with advancing age. Apart of this increase in CAL is down to gingival recession which itself
is an indicative of progressing periodontal deterioration (Billings et al. 2018).
The exact mechanism by which advancing age predisposes to periodontitis is not known. However, ageing is not considered to be a direct contributor to the development of periodontitis. This is supported by lack of association between age-related changes in periodontium, such as higher fibrotic content or decrease vascularity of periodontium, and risk of periodontitis. Ageing is proposed to elevate the risk of periodontitis through age-related factors such as presence of systemic diseases, malnutrition, decreased dexterity and decreased frequency of regular dental visits (Persson 2017).

**Gender**

Men are 50% more likely to have periodontitis as compared to women. Moreover, risk of severe periodontitis among men is three times to that for women. The exact mechanism by which men are more prone to periodontitis is still poorly understood. It is proposed that higher prevalence of lifestyle and behavioral risk factors such as poor oral hygiene and smoking among men is mainly responsible for the difference in risk of periodontitis between genders (Genco & Borgnakke 2013).

2.1.7.2 Modifiable factors

**Systemic factors**

Systemic risk factors such as diabetes, obesity and use of medication for systemic diseases increase the risk of periodontitis. The exact mechanism by which individual systemic diseases contribute to the development of periodontitis is still poorly understood. However, it is suggested that systemic risk factors facilitate in the development of periodontitis by impairing metabolic control and causing dysregulation of immune response (Casanova et al 2014). The alterations caused by systemic factors in the immune system varies from mounting a deficient immune response against bacterial stimulus to the development of hyperactive inflammatory response (Silva et al. 2015).

**Diabetes**

Most widely accepted systemic risk factor for periodontitis is diabetes. The prevalence of periodontitis among individuals with diabetes is three times to that of general population. Moreover, individuals with diabetes are also more likely to develop severe periodontitis and undergo rampant destruction of periodontium (Preshaw et al. 2012). The impact of diabetes on periodontium is so pronounced that it is regarded as one of the complications of diabetes. Diabetes is proposed to establish a general
inflammatory state that contributes in the dysregulation of immune response mounted against plaque bacteria (Chapple et al. 2013).

**Obesity and metabolic syndrome**
Several studies indicate increased risk of periodontitis as a function of obesity and metabolic syndrome. Increasing evidence indicates that obesity do not only increase susceptibility to developing periodontitis, but obese individuals also demonstrate greater loss of clinical attachment as compared to controls. The mechanism by which obesity facilitates in the development of periodontitis is still under study. However, it is suggested that obesity predisposes to periodontitis partly by modulating the immune response and facilitating in the establishment of dysbiosis (Genco & Borgnakke 2013).

Metabolic syndrome is also proposed to be an independent risk factor for periodontitis. Indeed, individual metabolic changes such as hypertension, dyslipidemia and insulin resistance are all found to increase the risk of periodontitis. These metabolic disturbances are suggested to facilitate in the development of periodontitis by impairment of immune response and contributing to systemic inflammation (Reynolds 2014).

**Osteoporosis, low dietary calcium and vitamin D deficiency**
Osteoporosis is another systemic factor that has been shown to increase the risk of periodontitis. Many studies have demonstrated that systemic osteoporosis also effects the jaw bones and thereby contributes to tooth loss. Furthermore, it is suggested that osteoporosis facilitates tooth loss indirectly by increasing the likelihood of developing periodontitis. However, the exact nature and magnitude of the effect of osteoporosis on periodontitis remains unclear (Martínez-Maestre et al. 2010).

In addition to osteoporosis, low dietary intake of calcium and vitamin D deficiency have also been found to increase the risk of periodontitis and tooth loss. Calcium deficiency is also found to impact the severity of periodontitis. The exact mechanism by which either of these deficient states contribute to periodontitis are still poorly understood. However, impairment of bone metabolism is cited as one of the possible pathways by which calcium and vitamin D deficiency adversely impacts periodontal health (Nishida et al. 2000).
Medication
Different classes of medicines such as antihypertensive drugs, narcotic analgesics and antihistamines are associated with increased risk of periodontitis. Multiple mechanisms have been proposed by which different medicine impart increased risk of periodontitis. Among the most commonly observed oral effect of systemic medicines is decreased salivary flow (Al-Jehani 2014). Saliva is the primary defensive mechanism by which host resist and maintain the bacterial stimulus from dental plaque to a minimum. Decrease in the composition or volume of saliva significantly impairs plaque control and increases the risk of periodontitis (Mariotti & Hefti 2015). Another important class of drugs that increase the risk of periodontitis is calcium channel blockers. Calcium channel blockers are associated with gingival overgrowth which hinders plaque control by sheltering plaque in resultant pseudo periodontal pockets. This allows for the maturation of plaque that subsequently increase the risk of periodontitis (Scully 2003).

Life style factors

Poor oral hygiene
Lack of adequate oral hygiene measures facilitates deposition and maturation of plaque that triggers chronic inflammatory pathology of periodontitis (Albandar 2002). Local retentive factors such as mal-aligned teeth and ill-fitting restorations further contribute to increased risk of periodontitis by facilitating plaque retention and making oral hygiene measures ineffective (Loesche & Grossman 2001).

Smoking
Smoking is regarded as the single most important preventable risk factor for periodontitis. The prevalence of periodontitis among smokers is almost twice to that of non-smokers. Smoking do not only contribute to the development and progression of periodontitis but is also a strong determinant of severity of periodontitis (Nociti et al. 2015). The exact mechanism by which smoking increases the risk of periodontitis is still not clearly understood. However, smoking is suggested to cause changes in immune system such as decreased production of immunoglobulins and increased expression of reactive oxygen species (ROS), that increases periodontal tissue destruction (Johannsen et al. 2014).
Alcohol intake
Many studies indicate negative effect of alcohol intake on periodontal health. However, effect of alcohol intake varies between genders and amount of alcohol consumed. Alcohol intake have been found to cause more detrimental effects on periodontal health in men as compared to women. Moderate alcohol intake has been found to cause little to no adverse effect on periodontal health, however, excessive consumption of alcohol significantly increases risk of periodontitis (Kongstad et al. 2008). Alcohol intake is proposed to impact periodontal health by alteration of plaque composition towards a more pathogenic type and increased expression of pro-inflammatory cytokines (Suwama et al 2018).

Psychological Stress and Depression
In addition to its negative effects on general health, stress is a significant determinant of periodontal health. It has been found to incur a number of physiological changes that may directly or indirectly contribute to increased risk of periodontitis. One such change is decreased salivary flow that aids in dysbiosis and subsequent development of periodontitis (Reners & Brex 2007). Furthermore, stress has also been found to reduce the effectiveness of periodontal treatment (Bakri et al. 2013).

Another important factor that increases the susceptibility of developing periodontitis is depression. The exact mechanism by which depression contributes to the development of periodontitis is yet poorly understood. However, evidence suggests that depression significantly impairs immune response and adversely affects wound healing that can directly contribute to the development of periodontitis. Furthermore, depression is also likely to negatively affect lifestyle habits thereby indirectly predisposing to periodontitis (Reynolds 2014).

2.2 DEMENTIA AND COGNITIVE IMPAIRMENT

2.2.1 Dementia

2.2.1.1 Definition and prevalence
Dementia is a syndrome characterized by progressive deterioration of cognitive function. Extent of cognitive deterioration observed in dementia is well beyond age-related cognitive decline and is essentially accompanied by functional incapacitation or functional dependence which leaves
individuals dependent on caregivers for carrying out day to day activities. It is highly prevalent among the elderly, with 5-7% of 60 years old or older individuals affected by it worldwide. Old age is the most significant predisposing factor for dementia, with prevalence of dementia reported between 20-50% among 85 years or older individuals (Slavin et al. 2013, WHO 2017).

The effects of dementia extend beyond the affected individual, with significant social and psychological burden experienced by caregivers and family members. Several factors such as chronic systemic diseases including CVDs, are implicated as risk factors of dementia. Many extensively studied risk factors are non-modifiable in nature, however increasingly greater number of studies are now being carried out with focus on modifiable risk factors (LoGiudice & Watson 2014).

Cognition is the mental ability or function to acquire, process, utilize and implement information or knowledge. Cognition is not a single process but is a constellation of multiple domains such as memory, thinking, orientation, language and judgement among others. All or several of these are usually involved at the same time in the processing of each piece of information (Woodford & George 2007).

Dementia affects multiple cognitive domains, although the pattern, number of cognitive domains affected, and the extent of deterioration depends on underlying pathology (LoGiudice & Watson 2014). For instance, memory is most commonly and extensively affected cognitive domain in Alzheimer’s disease (Aggarwal et al 2015), while executive function is most commonly compromised in vascular dementia (Ying et al. 2016). In addition to functional dependence, cognitive deterioration is often accompanied with or preceded by behavioral and psychiatric symptoms such as agitation, anxiety, depression, delusions, hallucinations, sleep and appetite disturbances (Cerejeira et al. 2012).

Around 50 million people are affected by dementia worldwide, with around 8-10 million new cases encountered on yearly basis. These numbers are projected to increase significantly in the next few decades owing to the increase in the number of elderly individuals worldwide. According to one estimate, prevalence of dementia is projected to surpass 150 million by 2050 (WHO 2017). Owing to the personal, societal and socioeconomic cost, dementia stands out among the foremost healthcare challenges of present time. Additionally, lack of availability of effective treatment, strongly advocates
studies into determining the modifiable risk factors and subsequent development of preventive strategies (Koch & Jensen 2016).

2.2.1.2 Types of Dementia
A number of pathologies are implicated in the development of dementia. Most of these underlying pathologies either belong to the neurodegenerative or cerebrovascular class of diseases. However, other conditions such as HIV infection, thyroid diseases and normal pressure hydrocephalus are implicated as the etiological factor leading to the development of dementia (WHO 2012).

The underlying disease that contributes to the development of dementia forms the basis of classification of dementia into its subtypes. In many cases a single underlying disease is clearly delineated. However, in others more than one disease occurs simultaneously. Even in cases where a single underlying cause is identifiable, there may lie significant variability in its presentation. Furthermore, signs and symptoms between different types often overlap (LoGiudice & Watson 2014).

Alzheimer’s disease is the most prevalent type of dementia, with 60-70% of individuals having AD. AD is followed by vascular dementia (VaD) and dementia with Lewy bodies with each contributing between 10-20% of dementia cases (Tripathi et al. 2014). Other less common types of dementia include frontotemporal dementia, dementia due to Parkinson's disease, Creutzfeldt-Jakob disease and Huntington’s disease (Reith & Mühl-Benninghaus 2015) (Table 2).

**Alzheimer’s disease**
Alzheimer's disease is clinically characterized by deterioration of multiple cognitive domains, of which memory is most extensively compromised. Pathological findings include intracellular accumulation of tau protein in the form of neurofibrillary tangles and extracellular deposits of amyloid protein (Shanthi et al. 2015). The exact mechanism that leads to its development is still not clearly understood. However, neuroinflammation and oxidative stress are suggested to be important pathological processes in regard to the development of AD (Gurav 2014).

**Vascular dementia**
Vascular dementia is characterized by the presence of cerebrovascular lesions. It is further stratified into subtypes such as multi-infarct dementia, single infarct dementia and subcortical dementia among others (Benisty 2013, Lam et al. 2014). VaD often develops in individuals with a history of ischemic stroke, which is proposed to cause progressive cognitive deterioration if experienced repeatedly. Executive dysfunction and psychomotor slowing are usually the most pronounced cognitive changes in VaD (Iadecola 2013).

Dementia with Lewy bodies
Dementia with Lewy bodies (DLB) is characterized by the presence of abnormal protein inclusions of \( \alpha \)-synuclein within neurons. Other neuropathological changes seen in DLB includes deterioration of tegmental dopamine cell population and basal forebrain cholinergic population. Along with general deficit in cognitive domains, DLB presents with hallucinations, impairment of executive function and visuospatial dysfunction (Gomperts 2016).

Mixed dementia
Mixed dementia is a term reserved for cases of dementia where more than one underlying pathology is suspected to be present. In cases of mixed dementia, a dominant type of pathology can be identified. However, there can also be extensive overlapping of clinical characteristics, making the exact determination of contributory pathological processes difficult. Most commonly observed combinations in mixed dementia are of AD and VaD or AD with DLB (Bhogal et al. 2013).
<table>
<thead>
<tr>
<th>Types of dementia</th>
<th>Neuropathological hallmarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Intercellular accumulation of beta amyloid and intracellular accumulation of tau protein</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>Cerebrovascular changes such as vessel blockage, hemorrhagic stroke and cerebral infarcts.</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Intracellular accumulation of alpha synuclein called Lewy bodies.</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Heterogeneous group of disorders characterized by protein accumulation in the frontal and temporal lobes (for example tau proteins or TDP-43 protein).</td>
</tr>
<tr>
<td>Mixed dementia</td>
<td>Overlapping of features pertaining to different types of dementia, for instance in mixed dementia with AD and VaD, protein accumulation is accompanied with cerebrovascular changes.</td>
</tr>
<tr>
<td>Parkinson’s disease dementia</td>
<td>Accumulation of alpha-synuclein primarily in substantia nigra as opposed to DLB. Neuropathological presentation can be variable, with some cases demonstrating accumulation of both alpha-synuclein and beta amyloid. Protein accumulation is accompanied by motor impairment.</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Spongiform changes in the grey matter. Caused by misfolded proteins (prions) that lead to misfolding and malfunctioning of other proteins throughout the brain matter.</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>Enlargement of ventricles owing to accumulation of cerebrospinal fluid (CSF) with little or no shrinkage of brain matter in initial...</td>
</tr>
</tbody>
</table>
stages, enabling it to be distinguished from other types of dementia.

2.2.2 Cognitive impairment

2.2.2.1 Definition and prevalence

Mild Cognitive Impairment (MCI) is defined as a pathological deterioration of cognitive function that does not meet the criteria for dementia or is not severe enough to be categorized as dementia. As per the definition, MCI has long been labelled as the prodromal phase of dementia or the intermediate state between healthy cognition and dementia. One of the significant differences between MCI and dementia is that functional capacity or functional independence is essentially preserved in MCI. There is a significantly greater risk of developing dementia among the individuals with MCI. The broad definition of MCI highlights the incomplete understanding of this pathology, which make its diagnosis and management difficult and prone to subjectivity (Langa & Levine 2014).

It is estimated that the prevalence of MCI is four times to that of dementia with prevalence values ranging between 3-42%. In general, rough estimates put the overall prevalence of MCI between 16-20% among the 65 years or older individuals which increases dramatically in subsequent decades (Roberts & Knopman 2013). Multiple factors such as systemic diseases and sedentary life style increase the risk of developing MCI (Eshkoor et al. 2015). The underlying etiology of MCI and the exact mechanisms that leads to its development are still poorly understood. Neurodegenerative diseases are proposed to be a primary cause of MCI (Aggarwal 2007). The diagnosis of MCI is based on clinical finding of cognitive impairment in one or more cognitive domains based on cognitive tests such as Mini mental scale examination (MMSE) or other standardized tests (Knopman et al. 2009).

Individuals with MCI carry a significantly higher risk of developing dementia, with 1 out of every 5 individuals with MCI developing dementia. Conversion rate of specific types of MCI differ significantly and there appears a pattern of higher conversion risk of certain types of MCI into specific forms of dementia, such as conversion of amnestic MCI into AD (Knopman & Petersen 2014). The exact mechanism and the risk factors that leads to the conversion of MCI into dementia is yet not
delineated. Despite significantly higher risk of developing dementia, some cases of MCI revert to normal cognitive state, while others may stabilize with limited or no discernible progression (Roberts et al. 2012). The factors that causes a specific group of individuals with MCI to develop dementia, while others are preserved are still under investigation (Trzepacz et al. 2014).

MCI not only increases the risk of dementia, but it also significantly impairs general quality of life (Knopman & Petersen 2014). This in addition to increased proportion of ageing population, personal and socioeconomic cost of its management makes it a major healthcare challenge (Eshkoor et al. 2014).

2.2.2.2 Types of Mild cognitive impairment (MCI)
MCI is broadly classified into two types, amnestic and non-amnestic. This categorization is based on the cognitive domains most prominently affected by the neurodegenerative process. Amnestic MCI is the cognitive impairment in which memory is greatly impaired, while other cognitive domains are either subtly involved or are persevered. Non-amnestic MCI refers to cognitive impairment involving deterioration of non-amnestic cognitive domains such as executive functioning, language and so forth. The two basic types are further classified into single and multiple domain subtypes. In single domain subtypes only one cognitive domain is affected, while cases of multiple domain subtypes involve more than one cognitive domain (Petersen 2011).

The prevalence of amnestic MCI is almost twice to that of non-amnestic types. Amnestic MCI carries a higher risk of conversion into AD as compared to any other type of dementia. Similarly, individuals with non-amnestic types of MCI are at greater risk of developing types of dementia other than AD. There is also increasing evidence suggesting that multi-domain MCI subtypes are more likely to progress into dementia as compared to single domain MCI subtypes (Petersen RC et al. 2010). Another important difference between the amnestic and non-amnestic MCI, is higher prevalence of behavioral changes in non-amnestic MCI (Mortimer et al. 2013).

2.2.3 Diagnostic criteria for Dementia and Mild Cognitive Impairment
The diagnosis of dementia and MCI is complex and based primarily on the clinical findings of cognitive impairment and its effects on functional independence. These two attributes form the core of the diagnostic criteria defined in standard diagnostic manuals such as Diagnostic and Statistical Manual
of Mental Disorders (DSM) and International Statistical Classification of Diseases and Related Health Problems (ICD) among others (American Psychiatric Association 2013). The general criteria for dementia and cognitive impairment in either DSM or ICD are similar. However, subtle differences pertaining to behavioral changes and involved cognitive domains that delineate between subtypes do impact the prevalence values and breakdown of different types (Wancata et al. 2007).

Findings from medical examination are supplemented with neuropsychological assessment, which provides a measure of the type and extent of the impairment. The neuropsychological assessment uses a battery of cognitive tests such as Mini-Mental State Examination (MMSE) or other more complex tests. Neuroimaging is also used which is helpful in identifying and quantifying pathological changes in the brain (Echavarri et al. 2012). More recent diagnostic criteria for research also take into account cerebrospinal fluid (CSF) biomarkers such as tau and β-amyloid proteins.

The diagnostic criteria for neurodegenerative disorders have evolved over time and are likely to undergo further refinement as the mechanisms leading to their development become clearer. There have been significant differences in the diagnostic criteria of dementia and MCI in DSM-5 as compared to previous versions. The term “dementia” was removed from DSM-5, and the heading of Delirium, Dementia, and Amnestic and Other Cognitive Disorders was replaced with Neurocognitive Disorders. The category of Major Neurocognitive Disorder was introduced, corresponding to the previous Dementia category as given in older versions of DSM (American Psychiatric Association 2013). Furthermore, a new category of Mild Neurocognitive Disorder was introduced that corresponds with the definition and presentation of MCI. No specific criteria for MCI had been listed in previous DSM versions.

The diagnostic criteria for Major Neurocognitive Disorder are based on 2 major clinical findings. Firstly, the subject should demonstrate cognitive deterioration of pathological nature in any cognitive domain, and secondly, cognitive deterioration needs to be severe enough to impair individual’s ability to carry out day to day tasks (Sachdev et al. 2014). The updated criteria in DSM-5 for dementia are different from earlier versions where deterioration of memory held key importance and required demonstration of deterioration of multiple cognitive domains for a formal diagnosis of dementia to be made. Although classical features of cognitive impairment and functional incapacitation are
demonstrated by all forms of dementia to varying degree, specific types of dementia are delineated on the basis of neuropathological findings inherent to each type (Hugo & Ganguli 2014).

The introduction in DSM-5 of more specific criteria for Mild Neurocognitive Disorder acknowledges the fact that more and more old individuals with cognitive decline seek medical care early, before they develop dementia. One important purpose of emphasizing MCI as a separate diagnosis has been to facilitate early diagnosis and treatment of the underlying disease, before it progresses to the more severe stage of dementia. In addition, it also acknowledges the fact that MCI may not always be progressive in nature. The diagnostic principle is similar to Major Neurocognitive Disorder or dementia except that in MCI, cognitive impairment is not severe enough to affect individual’s ability to carry out day to day task (Sachdev et al. 2015).

In addition to subjective assessment of cognition, neuropsychological assessment using standardized tests is recommended in DSM-5. The battery of cognitive tests not only aids in screening the individuals with cognitive deficits but also enables to calibrate degree of cognitive deficit that in turn facilitates in differentiating between MCI and dementia. Although DSM-5 does not specify exactly which battery of cognitive tests should be used, it provides some guidelines regarding the degree of cognitive deterioration likely to be experienced in major and mild neurocognitive disorders. Neuropsychological assessment falling between 1 to 2 standard deviation of normative mean is suggested to indicate mild neurocognitive disorder, while for major neurocognitive disorder the value lies 2 or more standard deviation below normative mean (Sachdev et al. 2015).

In general, for evaluation of cognitive function and assessing orientation, immediate memory, language, calculation, short-term recall and attention, MMSE is the most widely used test. Score ranges from 0 to 30, with a score of 24 or below suggesting dementia, although a threshold for MCI has not been universally established (Tombaugh & McIntyre 1992, Lancu and Olmer 2006). Additionally, other than MMSE, a range of more detailed and sensitive neuropsychological test batteries are available. Majority of these tests assess multiple cognitive domains; however, a number of cognitive tests also evaluate specific cognitive domains that help in distinguishing between different types of cognitive impairment. For instance, Wechsler memory scale –Revised (WMS-R) is used for assessment
of memory, whereas Boston naming test is employed for assessing language and executive function can be specifically assessed through digit symbol substitution test (Stokin et al. 2015).

2.2.4 Risk factors for Dementia and Mild cognitive impairment

Dementia and MCI are regarded as multifactorial conditions. Many demographic, systemic and lifestyle factors are implicated for contributing to the overall risk of dementia and MCI. Many of these factors often occur and interact across the entire life span and are through various pathways proposed to result in cognitive deterioration. While some of these risk factors such as age and family history are non-modifiable, many modifiable risk factors such as diabetes, CVDs and various lifestyle factors have been identified (Table 3). Owing to the debilitating nature of these pathologies and lack of availability of effective treatment, modifiable factors are a subject of several epidemiological studies looking into the preventive strategies for dementia and MCI (Sindi et al. 2015).

2.2.4.1 Non-modifiable risk factors

Demographic factors
Demographic factors such as age and gender significantly increase the risk of dementia and cognitive impairment.

Age
Age is regarded as the strongest risk factor for either condition with majority of the cases occurring in 6th decade of life or thereafter (Kalantarian et al 2013). The incidence of dementia increases dramatically with age, doubling in less than 6 years. Indeed 70% of all dementia cases occur in 75 years or older individuals (Fratiglioni et al. 2000). The incidence of dementia is found to increase from just 3.1 cases per 1000 among the 60-64 years old age group to 175.0 cases per 1000 among the 95 years or older age group (WHO 2012). The same pattern seems to be followed by MCI. Although the incidence values for MCI varies from 5.1 to 168 per 1000 persons, as in the case of dementia, incidence of MCI tends to increase with advancing age (Roberts & Knopman 2013).

Gender
Gender is also found to independently influence the risk of dementia and MCI. Women are found to be at a greater risk of dementia, with factors such as higher life expectancy and hormonal changes after menopause being suggested as possible explanations (Rocca et al. 2014). Contrary to dementia several studies have reported greater risk of MCI in men, with men being twice more likely to have MCI than women. Higher prevalence of systemic diseases and relatively less healthy life style such as increased alcohol consumption and smoking among men as compared to women have been suggested as potential causes of increased risk of MCI among men (Roberts et al 2012). However, more studies are needed to conclusively determine the role of gender differences in the risk of cognitive impairment.

**Genetic factors**
Genetic factors such as familial aggregation and different individual genes are found to increase the risk of dementia and MCI. Studies have reported 25 to 50% increase in risk of dementia among individuals with family history of dementia (Milne et al. 2008), while the risk of cognitive impairment also substantially increases in individuals with family history (Locke et al. 2009). Furthermore, the degree of cognitive deterioration may be more pronounced in cases with familial aggregation (Scarabino et al. 2016).

Several different genes are implicated in increasing the risk of developing dementia. This is particularly true for AD, in which presence of ε4 allele of Apolipoprotein E (ApoE ε4) is regarded as an established risk factor, with at least 15-20% of all cases of dementia attributed to it. Moreover, ApoE ε4 is found to decrease the age of dementia onset and also adversely affect its responsiveness to interventions (Teruel et al. 2011).

### 2.2.4.2 Modifiable risk factors

**Cardiovascular and metabolic risk factors**
Systemic factors such as cardiovascular and metabolic diseases, significantly add to the risk of dementia and MCI. Although multiple mechanisms have been postulated to explain for the effect of systemic diseases on cognition, the exact mechanisms by which systemic diseases contribute to the development of cognitive deterioration are not fully clarified. Regardless of the systemic risk factor
involved, increasing evidence suggests that significant reduction in the risk of cognitive deterioration may be possible through the management of systemic diseases (Baumgart et al. 2015).

**Cardiovascular diseases**

A wide range of cardiovascular pathologies such as atrial fibrillation, thrombotic events, heart failure and hypertension increase the risk of dementia and cognitive impairment (Da la Torre 2012, Wand et al. 2015). A number of possible mechanisms such as cerebral hypo-perfusion and cerebral infarction among others are cited as leading to subsequent cognitive deterioration (Etgen et al. 2011). Additionally, the time frame during which cardiovascular risk factors develop, appears to be important for the risk of late-life cognitive deterioration. Risk factors such as hypertension in midlife seem to be consistently associated with increased risk of dementia and cognitive impairment later on. Studies on hypertension at older ages have reported conflicting results. However, further studies are required to conclusively determine the magnitude and time span of effects of CVDs on cognition (Corrada et al. 2017).

**Diabetes**

Diabetes is another important condition that independently elevates the risk of dementia and MCI. This is particularly true for vascular dementia with studies reporting up to 60% increased risk of vascular dementia in people with diabetes. Furthermore, diabetes is also found to increase the risk of progression of MCI to dementia (Chatterjee et al. 2016). It is suggested that cerebrovascular disturbances produced by diabetes explain the increased risk of cognitive decline and dementia. Additionally, impairment of metabolic control is also suggested to contribute towards the adverse effects of diabetes on cognition (Hardigan et al. 2016).

Diabetes also demonstrates an association with AD. Individuals with diabetes carry significantly greater risk of developing AD, with studies indicating a link between diabetes and accumulation of amyloid (Chung et al. 2018). Multiple mechanisms such as impairment of insulin signaling, oxidative stress and mitochondrial dysfunction are attributed to the impact of diabetes on elevating the risk of AD. However, further studies are required to clearly elucidate the exact mechanisms (Yang & Song 2013).
Obesity and metabolic syndrome

Obesity and metabolic syndrome have been reported as significant risk factors for dementia and cognitive impairment (Miller & Spencer 2014, Rizzi et al. 2014, Tynkkyen et al. 2016, Ylilauri et al. 2017). The effect of obesity on the risk of dementia appears to be age-dependent. Obesity in midlife significantly elevates the risk of cognitive deterioration, but like hypertension its contribution to the development of cognitive deterioration is less clear at older ages (Singh-Manoux et al. 2018).

A decline in body mass index has been reported to occur over time in people who develop dementia later on. This may explain why some studies have reported contradictory findings, indicating that higher body mass index at older ages may be protective against dementia (Qizilbash et al. 2015). Further studies are still needed to determine the exact nature and magnitude of the effect that obesity has on cognitive deterioration.

Metabolic syndrome is also suggested to elevate the risk of cognitive deterioration. Indeed, different constituent pathological disturbances seen in metabolic syndrome, such as dyslipidemia, are found to be risk factors for cognitive deterioration (Liu et al. 2015, Salameh et al. 2016).

The biological mechanisms behind the impact of obesity and metabolic syndrome on dementia risk are still poorly understood. They are suggested to increase the risk of cognitive deterioration through their effects on general health. Obesity and subsequent increased adiposity increase the risk of developing other systemic pathologies, that are in turn are established risk factors for cognitive deterioration (Gustafson 2006). Furthermore, obesity is also found to be associated with brain atrophy (Ho e al. 2010).

Lifestyle, psychological and other risk factors

Early life adversities

Factors indicative of early life adversities such as low education and poor socioeconomic status and related factors significantly increase the risk of dementia and cognitive impairment. Both poor socioeconomic status and low education can affect lifestyle, access to health care services and awareness regarding diseases and corresponding adoption of preventive measures, thereby contributing to an individual’s risk of multiple pathologies including dementia (McDowell et al. 2007).
The exact pathological mechanisms by which early life adversities contribute to the development of cognitive deterioration are not fully known. However, they are believed to affect brain development and compromise attainment of cognitive reserve that in turn decreases the resistance against neuropathological changes leading to the development of cognitive deterioration (Russ et al. 2014). Moreover, they are also proposed to increase the risk of dementia and cognitive impairment by increasing the likelihood of developing systemic diseases that in turn independently increase the risk of cognitive deterioration (Xu et al. 2014).

**Smoking**

Smoking is one of the most commonly implicated life style factors in cognitive deterioration. Current smokers carry significantly higher risk of dementia and MCI as compared to non-smokers and former smokers. The mechanisms by which smoking imparts adverse effects on cognition are not fully clear, although the impact of smoking on cardiovascular health may at least partly explain the effects. However, the effects are suggested to be of reversible nature, evident by reduction of dementia risk upon smoking cessation. The reduction in dementia risk on smoking cessation is significant, with formers smokers carrying almost same risk of dementia as non-smokers (Zhong et al. 2015).

**Alcohol intake**

Alcohol intake is another important lifestyle factor with significant bearing on cognition. Current evidence indicates that alcohol exerts a range of effects on cognition which depends on the quantity of alcohol consumed. Both heavy alcohol intake and complete abstinence from alcohol have been reported to increase the risk of cognitive decline, while mild to moderate alcohol intake suggested to impart a certain degree of protection against cognitive impairment (Kim et al 2016, Sabia et al. 2018).

Depression of central nervous system, neurotoxicity and impairment of cerebrovascular function are implicated as possible pathways by which heavy alcohol intake leads to detrimental effects on cognition (Wilhelm et al. 2015). However, the mechanism by which abstinence from alcohol increases the risk of cognitive deterioration and the pathway by which mild to moderate alcohol consumption provides a protective effect are still not known (Wood et al. 2016, Sabia et al. 2018).
**Depression**

Several studies have indicated that the risk of cognitive deterioration is significantly higher in individuals with depression. Furthermore, there is also evidence that indicates increase in severity of depression increases the severity of cognitive deterioration (Gutzmann & Qazi 2015). The exact part that depression plays in cognitive deterioration is not clear, although, studies have observed some similarities in brain changes in people with depression and those with dementia, indicating a likely link between the pathological entities (Bennett & Thomas 2014). However, depression may also be a consequence of the neurodegenerative disease process, and one of the first symptoms to accompany the development of cognitive impairment (Zulkifly et al. 2016).

**Head injury**

History of head injury is another factor linked with increased risk of dementia. The risk is found to be particularly significant in cases where head injury was accompanied with loss of consciousness. Repeated minor head injuries such as concussion have been found to produce structural changes in the brain. These structural changes compounded over time are believed to elevate the risk of developing dementia (Hugo & Ganguli 2014).
Table 2: Risk and protective factors for Dementia and Cognitive impairment

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Protective factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-modifiable:</strong></td>
<td><strong>Non-modifiable:</strong></td>
</tr>
<tr>
<td><strong>Demographic factors:</strong></td>
<td><strong>Genetic factors:</strong></td>
</tr>
<tr>
<td>Age</td>
<td>Different genes such as ApoE ε2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Genetic factors:</td>
<td></td>
</tr>
<tr>
<td>Different genes particularly ApoE ε4</td>
<td></td>
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<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td><strong>Modifiable:</strong></td>
<td><strong>Modifiable:</strong></td>
</tr>
<tr>
<td><strong>Systemic factors:</strong></td>
<td><strong>Socioeconomic factors:</strong></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>High education</td>
</tr>
<tr>
<td>Stroke</td>
<td>High income</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Hypertension</td>
<td></td>
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<td>Obesity</td>
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<tr>
<td><strong>Lifestyle factors:</strong></td>
<td><strong>Lifestyle factors:</strong></td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>Physical activity</td>
</tr>
<tr>
<td>Smoking</td>
<td>Participation in cognitively stimulating activities</td>
</tr>
<tr>
<td>Heavy alcohol intake</td>
<td>Participation in social activities</td>
</tr>
<tr>
<td>Unhealthy dietary habits such as diets rich in saturated fats</td>
<td>Mild to moderate alcohol intake</td>
</tr>
<tr>
<td><strong>Others:</strong></td>
<td><strong>Pharmacological agents:</strong></td>
</tr>
<tr>
<td>Depression</td>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Psychological stress</td>
<td>Statins</td>
</tr>
<tr>
<td>Traumatic head injury</td>
<td>NSAIDs</td>
</tr>
</tbody>
</table>
2.2.5 Possible prevention strategies for Dementia and Mild cognitive impairment

Many modifiable factors have been proposed to significantly reduce the risk of dementia and cognitive impairment (Savica and Petersen 2011). Among these factors, physical activity and higher education are found to be most impactful (Schlosser Covell et al. 2015, Mirza et al. 2016). Moreover, healthy dietary practices such as diets rich in omega 3 and antioxidants, bilingualism and participation in social and cognitively stimulating activities also render some protective effect against cognitive deterioration (Hu et al 2013, Ramakrishnan et al. 2017, Zhou et al. 2018).

The exact mechanism by which these factors provide protection against cognitive deterioration are still poorly understood. Healthy lifestyle practices such as physical activity and Mediterranean diet are believed to prevent metabolic disturbances and systemic inflammation that are in turn regarded as independent risk factors for dementia and cognitive impairment (Petersson and Philippou 2016). Whereas, social and cognitively stimulating factors such as higher education, bilingualism, continuous learning and social activities are suggested to render protective effect against cognitive deterioration by means of ’cognitive reserve’ (Paillard-Borg et al. 2009). Cognitive reserve is a term referring to the individual’s ability to tolerate or cope with the pathological changes by means of the way in which cognitive tasks are processed and performed (Russ et al. 2013).

In addition to lifestyle factors, evidence suggests that a number of pharmacological agents such as antihypertensive drugs, statins and anti-inflammatory agents like non-steroidal anti-inflammatory drugs (NSAIDs) may provide protective effect against dementia and cognitive impairment (Pan et al. 2018, Tan et al. 2018, Xue ta al. 2018). The underlying principle in the proposed effect of these agents is to reduce the risk of systemic diseases that in turn are risk factors for cognitive deterioration. However, the evidence regarding rigorous use of any of these agents in preventive regimens is not enough. Indeed, some studies have also produced contradictory results, especially in case of NSAIDs, where use of suggested pharmacological agents in old age may predispose to a greater risk of cognitive deterioration. Furthermore, the dosage, duration of use and time span during which they may render protective effect are still under investigation (DeLoach & Beall 2018).
Several clinical trials involving different lifestyle changes or pharmacological agents have been conducted. Although some positive effects have been observed, the magnitude of the effect has not been of much practical significance (Sindi et al. 2015). There are 3 main reasons cited for this limited success. Firstly, most of the trials were focused on determining the effect of targeting a single risk factor, which does not consider the multifactorial nature of dementia. Secondly, dementia is a chronic pathology that results from the interplay of several risk factors over a life span. Thereby, preventive measures are also needed to be applied with a life course perspective, rather than administering them in old age when the underlying pathology may already have been in development for years (Mangialasche et al. 2012).

Thirdly, several risk factors such as hypertension and obesity seem to have age- or time-dependent effects, suggesting that there may be an optimal time window when preventive interventions need to be administered to achieve maximum benefit (Richard et al. 2009, Corrada et al. 2017, Singh-Manoux et al. 2018). Moreover, methodological limitations such as small sample size and short duration of the study are reasoned for the inconclusive effects (Mangialasche et al. 2012).

**2.2.5.1 Multi-domain trials in Dementia prevention**

Several recent clinical trials have attempted to prevent dementia and MCI by applying multidomain preventive interventions that aim to target multiple risk factors simultaneously. Examples of such major trials include Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), Multidomain Alzheimer Preventive Trial (MAPT) and the Prevention of Dementia by Intensive Vascular Care (PreDIVA). These trials are based on controlling for systemic and vascular factors in conjunction with introduction of lifestyle changes. Lifestyle changes comprise physical activity, healthy nutrition, social and cognitively stimulating activities that have been suggested to increase resilience against cognitive deterioration (Andrieu et al. 2011).

FINGER is a multidomain, multicenter interventional study conducted on 1260 individuals. It is the first large 2-year trial that has shown significant positive effects on cognition for a multidomain lifestyle intervention. The intervention comprised of vascular risk factors management, nutritional guidance, physical activity and engagement in social and cognitively stimulating activities (Ngandu et al. 2015). MAPT is a French multidomain, multicenter interventional study conducted on 1680
individuals. It also tested the efficacy of multidomain intervention including omega 3 supplementation in reducing the risk of dementia (Tabue-Teguo et al. 2018).

PreDIVA was another interventional study conducted on 3534 individuals that adopted multidomain strategy against dementia prevention. It analyzed the difference in risk of dementia between individuals receiving standard care for cardiovascular factors and individuals that received intensive vascular care. Intensive care regimen adopted in PreDIVA managed cardiovascular factors through multidomain strategy including medication, nutritional and lifestyle alterations (Moll van Charante et al. 2017). The MAPT and PreDIVA trials have several differences from FINGER, for example different target population and intensity of the multidomain intervention. These 2 trials did not show a significant impact on the main cognitive outcome (specific cognitive tests in MAPT, and dementia in PreDIVA).

3 AIMS AND METHODS

3.1 AIMS

3.1.1 General Objective
The general objective was to conduct a systematic review of original research articles that assessed the association between periodontitis and dementia. This review also aimed to study the role of periodontitis in the development of cognitive impairment. Due to the limited number of studies that were published at the time when the search strategy for this review was undertaken, all the studies evaluating periodontitis against cognitive decline, mild cognitive impairment, memory impairment and cognitive dysfunction were included in this review.

All the studies, pertaining to various endpoints of cognition were addressed under the main outcome of cognitive impairment, to assess the effect of periodontitis on cognitive impairment or on cognition in general. The assessment of the effect of periodontitis on cognition was carried out to assess contribution of periodontitis in the development of mild cognitive impairment which in turn increases risk of dementia (Petersen et al. 2001). This might render more insight into the impact of periodontitis on the overall continuum extending from healthy cognition right up to dementia.
3.1.2 Specific Objectives

This systematic review has following specific objectives:

1. To study whether periodontitis is a risk factor for dementia.
2. To study whether periodontitis is a risk factor for cognitive impairment.
3. To assess quality of evidence of studies evaluating the association between periodontitis and dementia.
4. To assess quality of evidence of studies evaluating the association between periodontitis and cognitive impairment.

3.1.3 Novelty compared to previous reviews

Although in the past few years, few reviews addressing the association of periodontitis and dementia have been conducted (Shen et al. 2016), most of them evaluated the role of periodontitis on the progression of dementia. Furthermore, as to our knowledge none of the reviews solely focused on longitudinal studies and included only a handful of studies with different study designs. This review focuses on longitudinal studies and includes more recent studies compared to previous reviews. Additionally, this review also focuses on studies assessing association between periodontal health and cognitive impairment. Furthermore, quality assessment of the included studies was also carried out to evaluate the overall quality of evidence that is currently available in regard to the role of periodontitis on cognition.

3.2 METHODOLOGY

This systematic review was limited to observational longitudinal studies. Studies that directly assessed association between periodontitis and dementia were searched on PubMed and Scopus. The search was restricted to English language publications and was conducted by using keywords “PERIODONTITIS”, “GINGIVITIS”, “TOOTH LOSS”, “DEMENTIA”, “PROSPECTIVE”, “RETROSPECTIVE”, “COHORT”, “FOLLOW UP” and “LONGITUDINAL”.

The same search strategy was further expanded with search terms like “MEMORY IMPAIRMENT”, “COGNITIVE IMPAIRMENT” and “COGNITIVE DETERIORATION” to retrieve studies that were primarily studying the role of periodontitis in the development of cognitive impairment. Detail of the search strategy is given in Table 4. Qualitative assessment of included studies was also conducted as
part of the review. The included studies were evaluated on four major domains and one minor domain to determine overall quality of each study and risk of bias in each study. A cumulative grading was assigned to each study based on grades attained in individual domains.

### 3.2.1 Inclusion criteria
Following is the inclusion criteria that was defined for this review:

- Longitudinal observational studies.
- Studies that recruited individuals without dementia at baseline. Studies with a mix of cognitively healthy individuals and individuals with cognitive impairment at baseline were also included if they conducted a separate analysis for incident dementia and incident cognitive impairment.
- Studies having periodontitis as the exposure (either assessed directly or evaluated through specifically justified proxy measures such as tooth loss).
- Dementia as the outcome of interest (for part of the review assessing periodontitis as a risk factor for dementia) and cognitive impairment as the outcome (for part of the review assessing periodontitis as a risk factor for impairment).
- Studies having a well-defined criterion for diagnosis of exposure and outcome.

### 3.2.2 Exclusion criteria
Cross sectional studies and studies that recruited individuals with dementia at baseline were excluded.

Table 3: MEDLINE search strategy PubMed July 2017 (run on date 18.07.2017)

```
((periodontitis) OR gingivitis) OR tooth loss

(((cognitive impairment) OR dementia) OR memory) OR cognitive deterioration

(#1 AND #2)
((((periodontitis) OR gingivitis) OR tooth loss)) AND (((cognitive impairment) OR dementia) OR memory impairment) OR cognitive deterioration

((((cohort) OR prospective) OR longitudinal) OR follow up) OR retrospective

(#3 AND #4)
```
3.3.3 Quality assessment

Due to lack of availability of standardized validated tools for quality assessment of longitudinal studies, method employed by Shamliyan et al (2011) was modified to meet the specific requirements of this review. The quality assessment was undertaken in four major domains and one minor. Grades in individual domains were combined to produce overall grading for each study.

Following are the domains in which each study was assessed:

2. Assessment of Exposure (Periodontitis): based on diagnostic method(s) and criteria used for evaluation of periodontitis.
3. Length of follow up period/study duration.
4. Assessment of Outcome (Dementia and Cognitive impairment): based on diagnostic method(s) and criteria used for the evaluation of outcome.
5. The minor domain is drop out or attrition of study participants.

3.3.3.1 Systematic evaluation of studies

Population representativeness

The representativeness of study population was based on 3 subdomains, age, random or non-random selection and sample size. The subdomain of age was dichotomized into 2 groups, less than 65 years old and 65 years or older. We categorized it as such, due to better probability of assessing longer-term risk pertaining to chronic diseases such as dementia in younger individuals (less than 65 years old). Secondly, older individuals are also likely to present with multiple comorbidities that may confound association in question and offer significantly less time for follow up.

Furthermore, older individuals are also likely to have asymptomatic or preclinical disease (outcome) in question as prevalence of both dementia and cognitive impairment increases significantly after 65 years of age, making risk assessment in that age group less reliable and non-representative for majority of general population (Kalantarian et al 2013).
The cut-off point of 65 years, although commonly mentioned in the literature, is somewhat arbitrary and should be interpreted as such. Considering that chronic diseases such as dementia take decades to develop, individuals may remain clinically asymptomatic for a long time. This may also apply to individuals younger than 65 years.

The subdomain of random or non-random selection was stratified as such, due to inherent limitations of non-randomized subject selection such as reduced validity and limitations encountered in generalization of findings. Lastly, adequate cut-off for sample size was established at 1000, as cohort studies require larger sample size as compared to case-control studies to convey same degree of reliability that a case-control study would render with a smaller sample. Secondly, cohort studies evaluate rate of outcome rather than prevalence of outcome, which is much smaller than prevalence and thereby larger sample size is required in cohort studies to yield reliable findings (Tanaka et al. 2015).

Each study was graded as either “GOOD”, “MODERATE” or “LOW” depending on the following criteria:

- Age ≤65 years AND random selection AND sample size>1000 = Good (G)
- At least two out of: Age ≤65 years, random selection, sample size >1000 = Moderate (M)
- At least two out of: Age >65 years, non-random selection, sample size<1000 = Low (L)

**Exposure assessment (Periodontitis)**

The grading of this domain was based on method(s) or criteria used for the assessment of periodontitis. Each study was graded as “GOOD”, “MODERATE” or “LOW” for this domain.

a. GOOD: Studies with clinically-diagnosed periodontitis using standardized method of periodontal examination such as measurement of periodontal pocket depths (PPDs) and/or Clinical attachment loss (CAL) and/or alveolar bone loss (ABL) or as per the criteria highlighted in ICD.

b. MODERATE: Studies with clinically-diagnosed periodontitis using other non-specific objective measures of periodontal health like Gingival bleeding index (GBI), Plaque control index (PCI) and number of missing teeth recorded by dentist or other dental medicine professional.

c. LOW: Studies that assessed periodontal status based on self-reported data such as tooth count or presence of gingival bleeding.
Assessment of the Outcome (Dementia and Cognitive impairment)

Studies with dementia as the outcome were grouped separately from those studies that assessed periodontitis and cognitive impairment. The domain of outcome assessment was graded as either “GOOD” or “LOW”.

a. GOOD: Studies that used standard diagnostic criteria as underlined in DSM or ICD to infer diagnosis of dementia. In case of cognitive impairment validated diagnostic criteria signified use of standardized cognitive tests, such as MMSE, to determine the presence and degree of cognitive impairment.

b. LOW: Studies that did not diagnose outcome(s) of interest by employing standard diagnostic criteria or used poorly defined diagnostic criteria.

Length of follow-up period / Study duration

Although there is no standard study duration for optimal assessment of dementia risk factors, in general studies with longer study duration in the range of decades provide more reliable scientific evidence as compared to studies of shorter duration (Vincent et al. 2012). The following assessment was used for study duration:

a. GOOD: Studies that had a follow up period of 20 or more years.

b. MODERATE: Studies with a follow-up period of 10-19 years.

c. LOW: Studies with less than 10 years of follow-up period.

Loss of follow-up/ Drop out

Attrition is another important aspect that defines the quality of a longitudinal study. Higher degree of participant drop-out yields lower degree of reliability to the findings. Subsequently, a study may fail to add intended knowledge to the body of evidence and answer the question of interest (Hill et al. 2016). Significant loss to follow up could indicate differences between participants, and thus lead to overestimation of the effect of exposure onto the outcome (Howe et al. 2013).

Considering the outcomes under study and mean age of participants, each study was graded as “GOOD”, “MODERATE” or “LOW” as per the following criteria:

a. GOOD: Studies with dropout of 20% or less.
b. MODERATE: Studies with drop-out of 20-40%.
c. LOW: Studies with more than 40% drop-out.

**Overall quality of evidence**
Cumulative grading for overall quality of a study was derived by summation of grades in individual domains for respective studies. Each study was graded as either “GOOD”, “MODERATE” or “LOW” for overall quality. The overall grading for each study was derived as follows:

a. GOOD: “GOOD” in all major domains and “GOOD” or “MODERATE” in minor domain.
b. MODERATE: “GOOD” or “MODERATE” in all major domains but does not meet the criteria for good quality of evidence.
c. LOW: “LOW” in at least one major domain.

**4 RESULTS**
The specific search strategy produced 46 articles. After reviewing through the abstracts of each article 31 studies were identified. After going through the full text, 10 articles fulfilled the inclusion criteria (Figure 1). Five of these studies had dementia as the outcome (Stein et al. 2007, Arrive et al. 2012, Tzeng et al. 2016, Lee YL et al 2017, Lee YT et al. 2017), while five studies assessed association between periodontitis and cognitive impairment (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Okamoto et al. 2015, Naorungroj et al. 2015, Okamoto et al. 2017). The reference list of each study was hand-searched in order to capture any potential study that may have been missed by the adopted search strategy.
Figure 1: Search Results (Prisma flow diagram)
4.1 STUDIES WITH DEMENTIA AS THE OUTCOME

The studies assessing the association between periodontitis and dementia are given in Table 5.

4.1.1 Designs and settings

All five studies were population based, longitudinal studies (Stein et al. 2007, Arrive et al. 2012, Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017). Two studies were prospective cohorts (Arrive et al. 2012, Lee YT et al. 2017) and three were retrospective studies (Stein et al. 2007, Tzeng et al. 2016, Lee YL et al. 2017). Three studies were from Taiwan (Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017), one from France (Arrive et al. 2012) and one from US (Stein et al. 2007). Four studies had both male and female participants (Arrive et al. 2012, Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017), whereas one study had female participants only (Stein et al. 2007).

All three studies from Taiwan based their investigation on data from National health insurance research database (NHIRD) of Taiwan (Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017). The study from France recruited participants from Paquid dental study (Arrive et al. 2012), and study from US was based on participants from NUN study (Stein et al. 2007).

4.1.2 Study population and duration

Three studies were conducted on participants who were 65 years or older (Stein et al. 2007, Arrive et al. 2012, Lee YT et al. 2017), while two studies adopted more diverse age criterion (Tzeng et al. 2016, Lee YL et al. 2017), with one cohort comprising of 45 years or older participants (Lee YL et al. 2017), while one had participants aged 20 years or more (Tzeng et al 2016).

Two studies had a sample size of less than 500 participants (Stein et al. 2007, Arrive et al. 2012), while sample size of two studies lied between 5000 and 10,000 participants (Tzeng et al. 2016, Lee YT et al. 2017). One study had a sample size of more than 180,000 participants (Lee YL et al. 2017).

Three studies had a follow-up period of 10 years (Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017), whereas one study had a follow-up period of 12 years (Stein et al. 2007) and one 15 years (Arrive et al 2012).
4.1.3 Periodontitis assessment
All five studies defined periodontitis as deterioration of tooth supporting tissues (Stein et al. 2007, Arrive et al. 2012, Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017). In general, multiple measures such as tooth loss and PPDs were used to assess periodontal health. Three studies assessed periodontitis according to ICD criteria based on PPDs and other objective measures (Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017), while two studies used multiple oral health measures (Stein et al. 2007, Arrive et al. 2012). One study also used a questionnaire to supplement findings of objective measures (Arrive et al. 2012).

4.1.4 Dementia assessment
Two studies used DSM criteria for the assessment of dementia (Arrive et al. 2012, Tzeng et al. 2016). One of these two studies diagnosed dementia according to DSM-IV R criteria (Tzeng et al 2016), while one used DSM- III R (Arrive et al 2012). Two studies diagnosed dementia using ICD-9 codes (Lee YL et al. 2017, Lee YT et al 2017), while one study-based assessment of dementia on the diagnostic criteria adopted in NUN study. NUN study based their diagnosis of dementia on cognitive test results (MMSE, DWR, etc.) and clinical finding of memory impairment. Furthermore, diagnostic criteria of NUN study included impairment in at least one non-memory cognitive domain and inability to perform day to day activities (Stein et al. 2007).

In all five studies participants were thoroughly examined by specialists to reach a conclusive diagnosis (Stein et al. 2007, Arrive et al. 2012, Tzeng et al. 2016, Lee TL et al. 2017, Lee YT et al. 2017). Clinical findings were supplemented with neuropathological evidence where available (Stein et al. 2007).

4.1.5 Periodontitis-Dementia association
Four studies reported higher risk of dementia for individuals with poor periodontal health (Stein et al. 2007, Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017). One study found inverse association between tooth loss and dementia onset, however this association only applied to subjects with lower education (Arrive et al. 2012).
Three studies that used ICD criteria for periodontal assessment found that individuals with periodontitis were significantly more likely to develop dementia as compared to those without periodontitis (Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017). One of these studies concluded that severity of periodontitis may be important in determining the risk of dementia pertaining to periodontitis (Lee YL et al. 2017). Although the study conducted by Stein et al (2007) showed a positive association between fewer teeth and dementia, it found no association between alveolar bone loss and dementia.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design and setting</th>
<th>Study population</th>
<th>Follow-up (years)</th>
<th>Periodontitis assessment</th>
<th>Dementia assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee YL et al. 2017</td>
<td>Retrospective population based, Longitudinal health insurance database (LHID 2000), National health insurance (NHI) Taiwan.</td>
<td>182,747 participants (97,802 participants with dental prophylaxis, 19,674 participants with no treatment, 59,898 with tooth extraction, 5,373 participants with intensive periodontal treatment), 45 years or older</td>
<td>10</td>
<td>ICD-9-CM codes 523.0–523.5</td>
<td>ICD-9-CM codes (290.X, 331.0).</td>
<td>Participants with severe periodontitis and those without treatment were at greater risk of developing dementia Reference group: participants with dental prophylaxis. HR: 1.14 (CI: 1.04 – 1.24) for participants with no treatment HR: 1.10 (CI: 1.04 – 1.16) for participants with tooth extraction. HR: 1.18 (CI: 0.97 – 1.43) for participants with intensive periodontal treatment.</td>
</tr>
<tr>
<td>Lee YT et al. 2017</td>
<td>Prospective population based,</td>
<td>6056 participants (3028 cases, 3028 controls),</td>
<td>10</td>
<td>ICD-9-CM codes 523.3–5</td>
<td>ICD-9-CM codes 290.0–290.4, 294.1</td>
<td>Periodontitis increased the risk of dementia. HR: 1.16 (CI: 1.01–1.32)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Follow-up</td>
<td>ICD-9-CM Codes</td>
<td>DSM</td>
<td>Description</td>
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<tr>
<td>Tzeng et al. 2016</td>
<td>Retrospective population based, Longitudinal health insurance database (LHID 2000), National health insurance (NHI), Taiwan</td>
<td>2,207 participants with periodontitis and 6,621 controls, 20 years or older</td>
<td>10</td>
<td>ICD-9-CM codes: 523.4 and 523.1</td>
<td>DSM-IV R</td>
<td>Participants with periodontitis were more likely to develop dementia as compared to controls. HR: 2.54 (CI: 1.297 - 3.352), p = 0.002</td>
</tr>
<tr>
<td>Arrive et al. 2012</td>
<td>Prospective population based, Paquid Dental study</td>
<td>405 participants (348 participants with PPDs measurements) 66-80 years (mean age 70)</td>
<td>15</td>
<td>Number of teeth, and temporo-mandibular joint function, 10 years</td>
<td>DSM-III R</td>
<td>No significant associations in participants with higher education. However, for participants with lower education tooth loss seemed to</td>
</tr>
</tbody>
</table>
Stein et al. 2007  
(PAQUIDENT). France  
Retrospective analysis of prospective participants, 75 - 98 years old (mean age 84 years)  
101 participants, 75 - 98 years old (mean age 84 years)  
12  
DMFT (decayed, missing, and filled teeth index) and questionnaire regarding dental health.

For 348 dentate participants bleeding on probing, PPDs using Community Periodontal Index criteria were noted.

have a protective effect against dementia. HR: 1.07 (CI: 0.57–2.02) for participants with 11 or more missing teeth and higher education. HR: 0.30 (CI: 0.11–0.79) for participants 11 or more missing teeth and lower education. HR: 0.42 (CI: 0.15–1.15) for PPDs for individuals with higher education, HR: 0.97 (CI: 0.29–3.19) for PPDs for participants with lower education.

MMSE, Delayed Word Recall, Boston
study, subset of NUN study, convenience sample - United States

Naming Test, verbal fluency test, Constructional praxis test.
The diagnosis of dementia was based on the criteria used in NUN study.

HR: 2.20 (CI: 1.1 - 4.5) for tooth loss
HR: 2.40 (CI: 0.86-6.6) for alveolar bone loss

OR: odds ratio, HR: hazard ratio, ICD: International Statistical Classification of Diseases and Related Health Problems, DSM: Diagnostic and Statistical Manual of Mental Disorder
4.1.6 Quality assessment of studies assessing Dementia

The quality assessment of the studies assessing association between periodontitis and dementia is given in Table 6. According to the derived criteria of quality assessment, two studies received “moderate” grading (Arrive et al. 2012, Lee YT et al. 2017), while three studies were assigned “low” grading (Stein et al. 2007, Tzeng et al. 2016, Lee YL et al. 2017). Two studies had moderate grading in population representativeness (Arrive et al. 2012, Lee YT et al. 2017) while three received low grading (Stein et al. 2007, Tzeng et al. 2016, Lee YL et al. 2017). Population representativeness turned out to be the main difference between the five studies, as all other domains produced same grading for all five studies.


Four studies assessed cognitive health and made subsequent diagnosis of dementia using the clinical criteria in ICD or DSM, yielding good grading to each of them for outcome assessment (Arrive et al. 2012, Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017). Even though one study used cognitive tests rather than ICD or DSM criteria for outcome assessment, it also yielded good grading for outcome assessment, as their derived criteria were similar with standardized criteria highlighted in diagnostic manuals. Furthermore, their clinical assessment of dementia was confirmed with neuropathological findings (Stein et al. 2007). None of the five studies had subject attrition or dropout of more than 20%, thereby all five studies were graded good for minor domain (Stein et al. 2007, Arrive et al. 2012, Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017).
## Table 5: Quality assessment of the studies assessing Dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Population representativeness</th>
<th>Study duration</th>
<th>Exposure assessment</th>
<th>Outcome assessment</th>
<th>Dropout</th>
<th>Overall quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee YL et al. 2017</td>
<td>L</td>
<td>M</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>L</td>
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<tr>
<td>Lee YT et al. 2017</td>
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<tr>
<td>Tzeng et al. 2016</td>
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<td>Arrive et al. 2012</td>
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<td>Arrive et al. 2012</td>
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</tbody>
</table>

### Major domains of quality assessment

1) Population Representativeness

- Age ≤65 years AND random selection AND sample size>1000 = Good (G)
- At least two out of: Age ≤65 years, random selection, sample size >1000 = Moderate (M)
- At least two out of: Age >65 years, non-random selection, sample size<1000 = Low (L)

2) Exposure Assessment

- Objective standard measurement using one or more of the following: CAL and/or PPDs, CPITN, radiographs or using the criteria highlighted in ICD= Good (G)
- Objective measurement using non-specific oral health indexes (GBI, PCI and number of missing teeth) = Moderate (M)
- Self-report = Low (L)

3) Length of follow up

- ≥20 years = Good (G)
- 10-19 years = Moderate (M)
- <9 years = Low (L)
4) Outcome Assessment

Valid if standard validated diagnostic criteria are used. If validated criteria are used it is taken equivalent to Good (G) and if non-validated criteria are used it is taken as low (L).

Minor Domain of quality assessment

5) Drop-out

- <20% = Good (G)
- 20% to 40% = Moderate (M)
- >40% = Low (L)

Overall quality of evidence

- Good (G) = “Good” in all major domains, AND “good” or “moderate” in the minor domain
- Moderate (M) = “Good” or “moderate” in all major domains OR does not meet the abovementioned requirements for good quality of evidence
- Low (L) = “Low” in at least one major domain.
4.2 STUDIES WITH COGNITIVE IMPAIRMENT AS THE OUTCOME

The studies assessing the association between periodontitis and cognitive impairment are given in Table 7.

4.2.1 Design and settings

All five studies were population-based, prospective studies (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017). Three studies were from US (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015) and two were from Japan (Okamoto et al. 2015, Okamoto et al. 2017). Four studies had both male and female participants (Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017), while one study had male participants only (Kaye et al. 2010).

The two studies from Japan used data from Fujiwara-kyo cohort (Okamoto et al. 2015, Okamoto et al. 2017), while one study from US was conducted on participants of Veterans Affairs Dental Longitudinal Study (Kaye et al. 2010), One study had participants from a subset of ARIC study (The Atherosclerosis Risk in Communities Study) (Naorungroj et al. 2015), whereas one study was based on Mexican American participants from the Hispanic Established Populations for Epidemiologic Studies of the Elderly (Reyes-Ortiz et al. 2013).

4.2.2 Study population and study duration

Four studies had a relatively narrow age range for participants, mainly focusing on elderly population (Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017). Three studies recruited participants who were 65 years or older (Reyes-Ortiz et al. 2013, Okamoto et al. 2015, Okamoto et al. 2017) whereas participants in one study were between 52 to 75 years at baseline (Naorungroj et al. 2015). Study from Kaye et al. (2010) adopted a wider inclusion criterion and recruited both middle aged and young adults, with the lowest age bound of 28 years at baseline.
Three studies had a sample size of less than 1000 participants (Kaye et al. 2010, Naorungroj et al. 2015, Okamoto et al. 2017), while sample size of two studies ranged between 2000 and 3500 (Reyes-Ortiz et al. 2013, Okamoto et al. 2015). Out of the five studies, three studies had a follow-up of 5 years (Reyes-Ortiz et al. 2013, Okamoto et al. 2015, Okamoto et al. 2017), whereas one study had a follow up of 8 years (Naorungroj et al. 2015) and one of 32 years (Kaye et al 2010).

4.2.3 Periodontitis assessment


Four studies assessed periodontal health objectively (Kaye et al. 2010, Naorungroj et al 2015, Okamoto et al. 2015, Okamoto et al. 2017), while one study used subjective data (Reyes-Ortiz et al. 2013). In addition to tooth count, four studies used PPDs (Kaye et al. 2010, Naorungroj et al 2015, Okamoto et al. 2015, Okamoto et al. 2017), while one study also had measurements on alveolar bone loss (Kaye et al. 2010). Kaye et al (2010) also used a questionnaire to supplement findings of PPDs, ABL and tooth count. Whereas Naorungroj et al (2015) conducted an interview as part of exposure assessment in addition to objective measures of PPDs and tooth count.

4.2.4 Cognitive impairment assessment

In three studies cognitive decline was the outcome. Cognitive decline was defined as change in cognition over time and was measured as the difference between baseline and final cognitive test scores (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015). Two studies defined outcome as mild memory impairment (MMI). In these studies, MMI referred to decline or impairment of memory while other cognitive domains remain intact. Furthermore, it was treated as a milder form of cognitive deterioration as compared to MCI (Okamoto et al. 2015, Okamoto et al. 2017). One of these studies analyzed MMI as the only outcome measure (Okamoto et al. 2017), while the other study also included cases of MCI in secondary analysis (Okamoto et al. 2015).
All five studies assessed cognitive status objectively by means of standardized cognitive tests (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017). Four studies used more than one cognitive test (Kaye et al. 2010, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017), while one study employed only one cognitive test for outcome assessment (Reyes-Ortiz et al. 2013). MMSE was the most commonly used cognitive test, employed by four of the five studies (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Okamoto et al. 2015, Okamoto et al. 2017), whereas three studies used recall test (Okamoto et al. 2015, Naorungroj et al. 2015, Okamoto et al. 2017).

4.2.5 Periodontitis-Cognitive impairment association

Overall results were conflicting on the association of periodontitis and cognitive impairment. The overall quality of evidence was low. Four studies did indicate positive association between low tooth count and cognitive impairment (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Okamoto et al. 2015, Okamoto et al. 2017). One of these studies reported positive association only in the subjects with positive status for ApoE ε4 (Kaye et al. 2010), while one reported positive association between rate of tooth loss and cognitive decline (Okamoto et al. 2017).

Two studies reported positive association between low tooth count and cognitive decline (Kaye et al. 2010, Reyes-Ortiz et al. 2013). One study reported positive association between low tooth count and MMI (Okamoto et al. 2017), while one study reported positive association between low tooth count and MMI and MCI (Okamoto et al. 2015). The study conducted by Naorungroj et al (2015) reported higher risk of cognitive decline in individuals with complete tooth loss.

Four studies analyzed association between PPDs and cognitive impairment (Kaye et al. 2010, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017). Three of these studies showed no association between PPDs and cognitive impairment either with cognitive decline (Naorungroj et al. 2015) or with MMI (Okamoto et al. 2017) or MMI and MCI (Okamoto et al. 2015). However, study conducted by Kaye et al (2010) observed positive association between PPDs and cognitive decline.
Furthermore, it also reported higher risk of cognitive decline as a function of alveolar bone loss (Kaye et al. 2010)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design and setting</th>
<th>Study population</th>
<th>Follow-up (years)</th>
<th>Periodontitis assessment</th>
<th>Cognitive impairment assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamoto et al. 2017</td>
<td>Prospective population based, Fujiwara-kyo study, Japan</td>
<td>537 participants (179 cases, 358 controls), 65 years or above.</td>
<td>5</td>
<td>Tooth count and PPDs using Community Periodontal Index criteria.</td>
<td>Mild memory impairment (MMI) - (MMI was defined as no impairment of ADL, normal general cognitive function: MMSE score ≥24, presence of objective memory impairment Recall test, score ≤ 1, and absence of depression) MMSE and Recall test.</td>
<td>No association between PPDs and MMI. Reference group: PPDs: CPI codes (0-3) and absence of ApoE ε4. OR: 0.96 (CI: 0.37–2.45) for code 4 and absence of ApoE ε4 OR: 0.73 (CI: 0.43–1.25) for code 4 and absence of ApoE ε4 OR: 1.01 (CI: 0.56–1.83) for code (0-3) and absence of ApoE ε4. No significant association between tooth loss and MMI, although presence of ApoE ε4 modulated the effect of tooth loss on MMI. Reference group: 9 or more teeth remaining and absence of ApoE ε4. OR: 0.99 (CI: 0.58–1.68) for 9 or less teeth remaining and presence of ApoE ε4.</td>
</tr>
</tbody>
</table>
Okamoto et al. 2015
Prospective population based, Fujiwara-kyo study, Japan

2158 participants. (2335 total, 177 edentulous), 65 years or older.

Tooth count and PPDs using Community Periodontal Index criteria.

Mild memory impairment (MMI) MM: normal cognitive function, no functional incapacitation but deterioration of memory as assessed by the 3-word delayed recall test in MMSE - “MMI status,” MMSE score of 24 or more, plus Recall

Significant association between having 17–24 remaining teeth and MMI, and total tooth loss (edentulism) and MMI. No association between PPDs and MMI.

OR: 2.82 (CI: 1.15–6.9) for 8 or less teeth remaining and presence of ApoE ε4
OR: 1.03 (CI: 0.59–1.81) for 8 or less teeth remaining and absence of ApoE ε4.

OR: 1.04 (0.74–1.47) for PPDs
Reference group: 25 or more teeth remaining.
OR: 1.58 (1.12–2.25) for 17-24 teeth present
OR: 1.17 (0.73–1.88) for 9-16 teeth present
OR: 1.08 (0.64–1.80) for 1-8 teeth present
Naorungroj et al. 2015
Prospective population based, Subset of ARIC study, United States
785 participants, 558 with PPDs assessment. 52–75 years

Self-reported tooth count, PPDs, bleeding on probing, interview, collection of gingival crevicular fluid and dental plaque
Periodontal disease was classified according to Biofilm gingival interface index

Cognitive decline. Delayed Word Recall (DWR), Digit Symbol Substitution (DSS) and Word Fluency (WF) test.

Tooth loss and periodontal disease did not predict greater cognitive decline. The exposure-outcome association was presented as a change in cognitive test scores against oral health measures

Beta estimate for PPDs (severe periodontitis) with corresponding standard error and p values:
DWR: −0.16 (SE: 0.21), p = 0.6040
DSS: −0.28 (SE: 1.56), p = 0.5165
WF: −0.50 (SE: 1.79), p = 0.6225
<table>
<thead>
<tr>
<th>Reyes-Ortiz et al.</th>
<th>Prospective population based, Mexican Americans participants, Hispanic Established Populations for Epidemiologic Studies of the Elderly (Hispanic EPESE), United States.</th>
<th>3032 participants (1967 participants in the final wave)</th>
<th>65 years or older</th>
<th>Self-reported tooth count</th>
<th>Cognitive decline, MMSE.</th>
<th>Fewer teeth was associated with greater cognitive decline over time as assessed through drop in MMSE score. Estimate change in MMSE over five year follow up period, negative sign indicates decline. Estimate= -0.12, (SE ± 0.05, p &lt;0.01) for overall drop in MMSE score.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>classification that comprises of PPDs and bleeding on probing to conclude presence and extent of periodontitis.</td>
<td>Beta estimate for PPDs (severe periodontitis) with corresponding standard error and p values as a function of time: DWR: 0.45 (SE: 0.27), p = 0.5655 DSS:0.55 (SE: 1.14), p = 0.7636 WF: −0.96 (SE: 1.17), p = 0.2173</td>
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<tr>
<td>2013</td>
<td></td>
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<tr>
<td>Kaye et al. 2010</td>
<td>Prognostic population based, Veterans Affairs Dental Longitudinal Study. (convenience sample, men only study), United States</td>
<td>597 participants, 28–70 years</td>
<td>32</td>
<td>PPDs, radiographic alveolar bone height, tooth count, new caries and restorations. Additionally, a questionnaire regarding oral hygiene practices was also administered.</td>
<td>Cognitive decline – fall of cognitive scores below the cut-off value (25 points or less than 90% of age and education specific scores on MMSE or less than 10 points on SCT).</td>
<td>Rate of tooth loss and periodontal disease progression indicated increased risk of cognitive impairment. Oral health measures against MMSE, SCT: HR: 1.03 (C:1.00 – 1.07), 1.03 (CI: 1.01, 1.06) - per additional tooth with alveolar bone loss progression/decade (tooth loss) HR: 1.04 (1.01, 1.09), 1.04 (1.01, 1.06) - per additional tooth with pocket depth progression/decade (PPDs) HR: 1.09 (1.01, 1.18), 1.12 (1.05, 1.18) - per additional tooth lost/decade (Alveolar bone loss) HR: 1.02 (0.97, 1.08), 1.05 (1.01, 1.08) - per additional tooth with new caries and/or restorations/decade.</td>
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OR: odds ratio, HR: hazards ratio
4.2.6 Quality assessment of studies assessing Cognitive impairment

The quality assessment of the studies assessing association between periodontitis and cognitive impairment is given in Table 8. All five studies received “low” grading (Kaye et al. 2010, Reyes Ortiz et al. 2013, Okamoto et al. 2015, Naorungroj et al. 2015, Okamoto et al. 2017). Unlike studies with dementia, studies concerning cognitive impairment were quite dissimilar in individual domains. Two studies received moderate grading for population representativeness (Reyes-Ortiz et al. 2013, Okamoto et al. 2015), while three were assigned low grading (Kaye et al. 2010, Naorungroj et al. 2015, Okamoto et al. 2017). Four studies were given low grade for study duration as each of these four studies followed participants for less than 10 years (Reyes-Ortiz et al. 2013, Okamoto et al. 2015, Naorungroj et al. 2015, Okamoto et al. 2017) while one study received good grade for study duration, as it followed the participants for up to 32 years (Kaye et al. 2010).

Four studies were assigned good grading for exposure assessment as they used standard measures such as PPDs for assessment of periodontitis (Kaye et al. 2010, Okamoto et al. 2015, Naorungroj et al. 2015, Okamoto et al. 2017), While study conducted by Reyes-Ortiz et al (2013) assessed periodontal status subjectively and received low grade for exposure assessment. All five studies received good grading for assessment of cognitive status. The cognitive health and subsequent diagnosis of cognitive impairment either as cognitive impairment (MMI or MCI) or cognitive decline was made using cognitive tests (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Okamoto et al. 2015, Naorungroj et al. 2015, Okamoto et al. 2017).

Three studies had subject attrition or dropout of less than 20% that yielded good grading for minor domain (Kaye et al. 2010, Naorungroj et al. 2015, Okamoto et al. 2017). Whereas two studies had 20% - 40% of subject attrition and were thus assigned moderate grading (Reyes-Ortiz et al. 2012, Okamoto et al. 2015).
Table 7: Quality assessment of studies assessing cognitive impairment

<table>
<thead>
<tr>
<th>Study</th>
<th>Population representativeness</th>
<th>Study duration</th>
<th>Exposure assessment</th>
<th>Outcome assessment</th>
<th>Drop out</th>
<th>Overall quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamoto et al. 2017</td>
<td>L</td>
<td>L</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>L</td>
</tr>
<tr>
<td>Naorungroj et al. 2015</td>
<td>L</td>
<td>L</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>L</td>
</tr>
<tr>
<td>Okamoto et al. 2015</td>
<td>M</td>
<td>L</td>
<td>G</td>
<td>G</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Reyes-Ortiz et al. 2013</td>
<td>M</td>
<td>L</td>
<td>L</td>
<td>G</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Kaye et al. 2010</td>
<td>L</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>G</td>
<td>L</td>
</tr>
</tbody>
</table>

Major domains of quality assessment

1) Population Representativeness
   - Age ≤65 years AND random selection AND sample size >1000 = Good (G)
   - At least two out of: Age ≤65 years, random selection, sample size >1000 = Moderate (M)
   - At least two out of: Age >65 years, non-random selection, sample size <1000 = Low (L)

2) Exposure Assessment
   - Objective standard measurement using one or more of the following: CAL and/or PPDs, CPITN, radiographs = Good (G)
   - Objective measurement using non-specific oral health indexes (GBI, PCI and number of missing teeth) = Moderate (M)
   - Self-report = Low (L)

3) Length of follow up
   - ≥20 years = Good (G)
   - 10-19 years = Moderate (M)
   - <10 years = Low (L)

4) Outcome Assessment
   Valid if standard validated diagnostic criteria are used.

Minor Domain of quality assessment

5) Drop-out:
   - <20% = Good (G)
   - 20% to 40% = Moderate (M)
• >40% = Low (L)

Overall quality of evidence

• Good (G) = “Good” in all major domains, AND “good” or “moderate” in the minor domain
• Moderate (M) = “Good” or “moderate” in all major domains OR does not meet the abovementioned requirements for good quality of evidence
• Low (L) = “Low” in at least one major domain.
5 DISCUSSION
In general, periodontitis appeared to contribute to the overall risk of dementia, whereas concerning cognitive impairment the results were less conclusive. However, lack of uniformity in the definition and assessment criteria of periodontitis and variability in study populations hindered cumulative assessment of studies and a more exact estimation of the effect size of periodontitis on the risk of dementia and cognitive impairment.

Furthermore, the lack of consensus in the definition and assessment of cognitive impairment made it difficult to assess in more detail the interplay between periodontal health and cognitive impairment. Multiple co-factors such as age (Stein et al. 2007, Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017), systemic diseases (Okamoto et al. 2015, Tzeng et al. 2016, Lee YL et al. 2017, Lee YT et al. 2017, Okamoto et al. 2017) and low socioeconomic status (Arrive et al. 2012, Tzeng et al. 2016, Lee YL et al. 2017) were observed to be significant modulators of the effect of periodontitis on dementia and cognitive impairment.

5.1 STUDIES ON PERIODONTITIS AND DEMENTIA

5.1.1 Overall findings
Currently available evidence suggests a positive association between periodontitis and dementia, with overall low to moderate quality of evidence. Four studies analyzed periodontitis in relation to incident dementia (Stein et al. 2007, Arrive et al. 2012, Tzeng et al. 2016, Lee YT et al. 2017), while one study assessed the possible effect of periodontitis severity on dementia risk (Lee YL et al. 2007). Though periodontitis appears to add to the overall risk of dementia, findings need to be interpreted with caution, give the limitations of the included studies and subsequently limited quality of evidence.

5.1.2 Measures of Periodontitis
Different measures, either individually or in combination, were used to assess periodontitis, including periodontal pocket depth, tooth loss and alveolar bone loss. PPDs indicated a positive association between periodontitis and dementia, whereas tooth loss provided conflicting results. While ABL had no significant effect on risk of dementia, only one study assessed periodontal health through alveolar bone loss (Stein et al. 2007).
5.1.3 Association between Periodontitis and Dementia based on periodontal pocket depths
Three studies, assessing difference in incident dementia between individuals with periodontitis and those without, used periodontal pocket depths (PPDs) to assess periodontal status (Arrive et al. 2012, Tzeng et al. 2016, Lee YT et al. 2017). Two of these studies were of moderate quality and both showed significant association between periodontitis and dementia (Tzeng et al. 2015, Lee YT et al. 2017), while the remaining study rendered low quality of evidence and observed no significant effect of PPDs on dementia (Arrive et al. 2012). Both studies that reported significantly greater risk of dementia proposed inflammation as a possible mechanism behind the impact of poor periodontal health on risk of dementia (Tzeng et al. 2015, Lee YT et al. 2017).

5.1.4 Association between Periodontitis and Dementia based on tooth loss
Two studies assessed periodontal status through tooth loss, with both studies providing low quality of evidence (Stein et al. 2007, Arrive et al. 2012). One of them showed significant association between tooth loss and dementia (Stein et al. 2007), while the other one observed no significant effect of tooth loss on risk of dementia (Arrive et al. 2012).

Indeed, the study conducted by Arrive et al (2012) observed a protective effect of tooth loss against dementia in individuals with lower education as compared to those with higher education. A possible explanation for this peculiar finding was provided, i.e. the tendency among the individuals with lower education to lose teeth earlier in life. Losing teeth earlier in life may subsequently decrease the inflammatory burden associated with periodontitis in the long run, thereby, somewhat decreasing the risk of dementia (Arrive et al. 2012). However, this finding should be interpreted with caution, given that low education is a strong risk factor for dementia (Beydoun et al. 2014).

Although tooth loss is a relevant proxy measure of periodontitis, tooth loss can have other causes such as dental caries or traumatic incidents. Therefore, conclusions regarding associations between periodontitis and incident dementia based on tooth loss alone should be carefully drawn.

5.1.5 Comparison between results based on different measures of Periodontal health
Although only one study of low quality of evidence indicated a positive association between tooth loss and dementia, 2 studies of moderate quality positively linking PPDs with dementia. The effect size of tooth loss on dementia risk was of higher magnitude (Stein et al. 2007), than that observed with PPDs (Tzeng et al. 2015, Lee YT et al. 2017).
Since tooth loss resulting from periodontitis is an indicator of periodontitis severity, this finding may suggest that more severe periodontitis is associated with higher risk of dementia. A possible mechanism could be the likelihood of increased inflammatory load due to increase in severity of periodontitis. While edentulism (complete tooth loss), by the same principle, may significantly lower the inflammatory burden contributed by periodontal tissue, other related factors such as decreased masticatory stimulation and nutritional deficits may contribute to higher dementia risk. It is also possible that the inflammatory burden produced by severe periodontitis prior to complete tooth loss may have already triggered pathological changes leading to cognitive decline and dementia.

However, severity of periodontitis is an important topic that should be further investigated in future studies on risk factors for dementia and cognitive impairment. Several methodological improvements will be needed to investigate the exact effects of tooth loss and edentulism as indicators for severity of periodontitis. For example, comprehensive recording of the cause of tooth loss should be undertaken, in addition to addressing the limitations of small sample size and inadequate study design. Both cause and time-period of tooth loss should be considered and accounted for, as the timeline of tooth loss would assist in estimating the past, present and cumulative life-long burden of periodontal disease and their significance in determining the risk of dementia and cognitive impairment. Another factor that should be considered is progression in PPDs or CAL, which are more objective indicators of severity of periodontitis.

### 5.1.6 Severity of Periodontitis

The possible role of periodontitis in dementia as a function of its severity, and the impact of periodontal treatment, are suggested by the study conducted by Lee YL et al (2017). They based their evaluation on the periodontal treatment delivered to participants at the baseline, which was representative of the severity of periodontal disease. This study observed that administration of no periodontal treatment or dental extraction (tooth loss) at baseline was related to higher risk of dementia as compared to dental prophylaxis or comprehensive periodontal treatment.

Individuals who required dental extraction at baseline were diagnosed with severe periodontitis. Although the periodontal status at the end of the study was not known, such individuals may have been more likely to develop severe periodontitis later on as well, which may explain their increased risk of dementia. On the other hand, individuals who received no dental treatment carried a slightly higher risk of dementia. The reasons why no or only limited dental treatment was administered are
not fully clear. If these individuals were diagnosed with mild periodontitis, their periodontal status may have worsened over time due to lack of treatment, thereby leading to a greater chronic inflammatory load. Whereas inflammatory burden may have been at least partly reduced in individuals with dental extraction, provided that their periodontal health remained stable thereafter.

Although conclusions regarding exact mechanisms cannot be drawn from this study, it seems that both presence of periodontitis and its severity have a role in determining overall risk of dementia. The importance of early and adequate treatment of periodontitis is also emphasized. Differences in the risk of dementia pertaining to past, present and cumulative life-long burden of periodontitis, as well as quality of treatment, should be further investigated.

5.2 STUDIES ON PERIODONTITIS AND COGNITIVE IMPAIRMENT

5.2.1 Overall findings
While a few of the findings suggested that poorer periodontal health may be related to cognitive impairment, non-significant results were reported as well (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017). Three of the five studies assessed periodontal status against cognitive decline (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015), while two studies evaluated periodontal status against risk of cognitive or memory impairment (Okamoto et al. 2015, Okamoto et al. 2017). Neither risk of cognitive decline nor memory impairment were significantly related to poor periodontal health (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017).

5.2.2 Measures of Periodontitis
Similar to the studies with dementia as the outcome, different measures including periodontal pocket depth, tooth loss and alveolar bone loss were used to assess periodontitis either individually or in combination. Assessment of periodontal status through PPDs against cognitive status showed no association between periodontitis and dementia (Kaye et al. 2010, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017), whereas tooth loss provided conflicting results (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017). The study conducted by Kaye et al (2010) observed a positive association between rate of alveolar bone loss and cognitive impairment. However, since this is the only study that assessed periodontal health through alveolar bone loss, findings need to be verified in further research.
5.2.3 Association between Periodontitis and Cognitive impairment based on periodontal pocket depths

Four of the five studies evaluated association between periodontitis and cognitive impairment based on periodontal pocket depths (Kaye et al. 2010, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017). Three of these studies found no correlation between PPDs and cognitive impairment (Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017), while one study indicated increased risk of cognitive impairment as a function of increased rate of periodontal pocket formation. Increased rate of periodontal pocket formation may infer presence of severe periodontitis and/or progression in severity at a faster pace, which may lead to a greater inflammatory burden and subsequently greater risk of dementia (Kaye et al. 2010).

5.2.4 Association between Periodontitis and Cognitive impairment based on tooth loss

All five studies assessed periodontitis through tooth loss (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Naorungroj et al. 2015, Okamoto et al. 2015, Okamoto et al. 2017), with three studies indicating positive association between tooth loss and cognitive impairment (Kaye et al. 2010, Reyes-Ortiz et al. 2013, Okamoto et al. 2015), while two studies observed no association (Naorungroj et al. 2015, Okamoto et al. 2017).

Among the three studies with positive correlation between periodontitis and cognitive impairment, one observed increased risk of cognitive impairment with higher rate of tooth loss. This may confer significance to severity of periodontitis in affecting the risk of cognitive impairment (Kaye et al. 2010). Another study reported significantly greater risk of cognitive impairment in individuals having 17-24 teeth in comparison to individuals with 25 or more teeth. But the effect was not significant with extensive tooth loss (16 or less teeth present), except for complete tooth loss (edentulism). A possible reason for this disparity in the association between extent of tooth loss and cognitive impairment may have been the mechanisms connecting periodontal health and cognitive impairment. And possible proportion of contribution made by each pathological mechanism relative to time and severity of periodontitis (Okamoto et al. 2015).

One study observed significant effect of tooth loss on cognitive impairment in individuals with ApoE ε4. The combined effect of tooth loss and ApoE ε4 was greater than the effect of either factor alone. ApoE ε4 is an established risk factor for AD and is proposed to increase amyloid induced inflammatory response and adversely affect the integrity of the blood-brain barrier (BBB). BBB provides a route for systemic inflammation to directly impact the brain that may increase the
likelihood of developing dementia. Tooth loss, as a consequence of severe periodontitis, has been suggested to contribute to the overall inflammatory burden (significantly added to by ApoE ε4) and subsequent risk of cognitive deterioration.

5.2.5 Variability in Cognitive assessment

When considering cognitive impairment, multiple factors may affect the assessment of its presence, progression and severity. Firstly, there was a lack of uniformity in definition of cognitive impairment in the included studies, which used either mild memory impairment, mild cognitive impairment or cognitive decline as outcomes. This lack of uniformity made comparisons of findings between different studies difficult.

Secondly, there are no universally accepted criteria for defining cognitive impairment, with differences between the procedures and tests employed in both research and clinical practice. This leads to significant variability in results of studies using cognitive impairment as the outcome. Thirdly, results from cognitive tests may be prone to misclassification (Wood et al. 2006). Cognitive tests are sensitive to factors such as age and educational level, which increase the difficulty of accurately assessing cognitive status and degree of cognitive impairment (Dellasega & Morris 1993).

Given that cognition is composed of multiple domains, it cannot be properly assessed by means of a single cognitive test (Synder et al. 2011). To better evaluate cognitive status, test batteries comprising multiple cognitive tests need to be applied. Also, cognitive test batteries need to include domain specific tests as well, to comprehensively assess specific cognitive domains in addition to global cognitive status (Lancu & Olmer 2006).

5.3 MECHANISMS

Dementia is a multifactorial pathology and it is likely that multiple different causal pathways concomitantly and/or synergistically contribute to its development. Periodontitis and dementia share several common risk factors such as various systemic diseases, old age and smoking. This indicates a complex interplay between multiple factors and mechanisms in determining the impact of periodontitis on cognition. Moreover, this also underlines the possibility of common pathways being part of the pathogenesis of periodontitis, cognitive impairment and dementia, and an interplay between theses pathologies (Cerajewska et al. 2015).
Several mechanisms have been proposed to explain the contribution of periodontitis to the development of dementia and cognitive impairment. Periodontitis may increase the risk of neurodegeneration by contributing to the development and/or maintenance of systemic inflammation. Systemic inflammation is an independent determinant of risk of cognitive deterioration and has been suggested to facilitate the development of neuroinflammation. Neuroinflammation is considered to be one of the central events in the pathogenesis and progression of cognitive deterioration (Gallart-Palau et al. 2017).

Periodontal pathogens are a source of constant low-grade bacteremia and subsequent trigger for the expression of proinflammatory cytokines. This low-grade focal inflammation constantly trickles into systemic circulation adding to the systemic inflammatory load produced by other chronic diseases such as CVDs and diabetes (Hajishengallis 2015). Periodontitis is independently associated with increasing systemic concentration of pro-inflammatory cytokines, evident by increased expression of systemic inflammatory markers such as C reactive protein (CRP) and tumor necrosis factor alpha (TNF-α) (Nilsson et al. 2017).

Systemic cytokines are known to cross the blood brain barrier (BBB) and elicit inflammatory response from glial cells. These systemic cytokines are suggested to either stimulate the glial cells to produce neuroinflammation by the release of local inflammatory mediators or add to the already existing inflammation elicited by other risk factors (Hasturk & Kantarci 2014). Inflammatory cytokines were also proposed to trigger production of β-amyloid protein and promote phosphorylation of tau protein, linking inflammation to protein accumulation and subsequent neurodegeneration (Cai et al. 2014).

Moreover, cytokines were suggested to facilitate neurodegenerative processes by multiple other mechanisms, such as, by causing direct neuronal damage and by increasing the permeability of BBB. The weakening of BBB has been suggested to provide direct access to periodontal pathogens and their products to the brain. Periodontal pathogens were proposed to be directly detrimental to brain, by starting a cascade of pathological changes leading to neuroinflammation and potentially neurodegeneration (Cai et al. 2014).

Other significant pathological changes brought about by the inflammatory process that may contribute to the development of cognitive impairment include decrease in the concentration of acetylcholine and increased expression of reactive oxygen species (ROS). Inflammatory cytokines
were found to significantly decrease the concentration of acetylcholine, both by inhibiting its production and by facilitating its breakdown. Increased expression of ROS was associated with deterioration of neuronal function, while reduction in the concentration of acetylcholine was suggested to produce atrophic changes in the brain (Cunningham 2013).

Tooth loss, a direct consequence of severe periodontitis, also independently increases the risk of dementia and cognitive impairment (Nilsson et al. 2014). Tooth loss may result in chronic nutritional deficits such as deficiency of Vitamin B, Vitamin E and antioxidants that adversely affect cognition, and, in the long run increase the risk of dementia. Furthermore, tooth loss was suggested to be directly detrimental to cognitive health by facilitating the development of atrophic changes in the brain. These atrophic changes are believed to result because of reduction in sensory input from masticatory apparatus (Kobayashi et al. 2018).

This is consistent with animal studies showing development of learning and memory deficits as a function of decreased masticatory stimulus due to tooth loss. Reduced brain stimulation has also been found to decrease the number of pyramidal cells in the brain leading to reduced acetylcholine levels in hippocampus and subsequently to memory deficit (Minn et al. 2013). Tooth loss was also associated with decreased cerebral blood flow and was found to affect oxygen concentration in the blood. Such changes in the cerebral circulation are also suggestive of adverse effects of tooth loss on brain (Tonsekar et al. 2017).

Another pathway through which periodontitis may contribute to cognitive deterioration is through the direct involvement of periodontal pathogens. Periodontal pathogens and their products may directly transmigrate through the blood brain barrier and invoke neuroinflammation. Periodontal pathogens are also believed to reach the brain through nerve plexus in the head region such as through the trigeminal nerve (Shoemark & Allen 2015). However, an infectious etiology of cognitive impairment and dementia seems to be a rather distant possibility particularly through periodontal pathogens, considering their relatively limited virulence, and the scarce amount of evidence supporting this hypothesis (Shaik et al. 2014).

However, the continuous presence of periodontal pathogens throughout life and subsequent constant presence of low-grade inflammation in periodontal tissues lends a certain degree of support to the possible role of periodontal pathogens in the overall risk of dementia. Periodontal pathogens have also been suggested to directly stimulate the innate immune system and glial cells to mount an
inflammatory response. Glial cells have an important role in the induction and maintenance of neuroinflammation. The glial cells in the elderly have been found to be hypersensitive and liable to produce an exaggerated inflammatory response, which is a common pathological trait for both periodontitis and dementia (Harding et al. 2017).

Studies have also observed increased expression of neurofibrillary tangles in mice, owing to lipopolysaccharide (LPS) induced chronic inflammation. LPS is a component of bacterial cell wall and its ability to effect protein metabolism in the brain supports a possible contribution of bacterial infection in the overall risk of neurodegeneration (Gurav 2014). Other possible pathways through which periodontal pathogens were proposed to increase the risk of dementia include increased expression of reactive oxygen species. Moreover, initial studies also suggest that periodontal pathogens might modulate the risk of dementia and cognitive impairment through their effects on adaptive immune system and host gene expression (Olsen et al. 2016, Carter et al. 2017). However, further studies are needed to clearly understand the role of periodontal pathogens in neurodegeneration and the exact mechanism by which periodontal health impact cognition.

5.4 STRENGTHS AND LIMITATIONS

To the best of our knowledge, this is the first review to assess the association between periodontitis and dementia based specifically on longitudinal studies. Secondly, this review also evaluates quality of evidence based on the risk of bias in each study. Another strength of this review is the assessment of association between periodontitis and cognitive impairment. The inclusion of cognitive impairment enables a clearer assessment of the possible impact of poor periodontal health on the continuum of cognition.

However, the limited number of available studies, variability in the definition and assessment of exposure and outcome and inconclusiveness of available evidence strongly supports the need for further studies to understand the links between periodontitis, cognition and dementia.

There is a possibility that some studies may not have been captured by the adopted search strategy, due to two main reasons. Firstly, the search strategy was limited to PubMed and Scopus, and secondly, search strategy was applicable to English language publications only. Furthermore, due to lack of validated assessment tools for quality assessment of longitudinal studies, assessment criteria were tailored for this review. This is inherently prone to limitations, such as limited consideration of measures relating to internal validity of studies.
Moreover, meta-analysis of the included studies was not conducted which may have been more informative in highlighting the effect of poor periodontal status on the continuum of cognition. The conductance of meta-analysis was deterred in part due to the variability in the assessment methods used to evaluate periodontal health as well as cognitive impairment. Furthermore, studies with cognitive impairment also lacked uniformity in terms of definition of the outcome of interest making statistical comparison difficult. Additionally, because of limited number of studies and heterogeneity in study populations meta-analysis was not undertaken.

5.5 CONCLUSION AND FUTURE DIRECTIONS
Due to limitations pertaining to each included study and the overall quality of evidence, the role of periodontitis in the development of dementia and cognitive impairment needs to be further explored. Nevertheless, it seems likely that periodontitis contributes to the overall risk of dementia and may even elevate the risk of cognitive impairment. Therefore, further well-designed longitudinal studies of adequate size and duration should be conducted to explore in more detail the magnitude of the effects and the underlying mechanisms. Comprehensive assessment of periodontitis, such as through use of multiple assessment measures including CAL, should be included in future studies.

Future studies should also consider various aspects of periodontitis such as its severity and past, present, and the cumulative burden of poor periodontal health, as possible factors affecting cognitive health. If possible, recording of both extent and cause of tooth loss should be carried out to better determine the extent of periodontal disease, and separately evaluate the effects of tooth loss as a consequence of periodontal disease and as an independent determinant of cognitive health. Any teeth replacement such as dentures and implants need to be noted, and their effects evaluated.

Concerning cognitive impairment as outcome, comprehensive assessment of cognition should be carried out through test batteries instead of single tests. Cognitive outcomes will need to be well defined according to standardized criteria to allow for comparisons to be made. Specific cognitive domains should be assessed in addition to global cognition, in order to determine potential effects of periodontitis on various cognitive domains. Such analyses may also facilitate in distinguishing the effects of periodontitis on various types of dementia.
It is likely that multiple pathological pathways are involved in conferring increased risk of dementia and cognitive impairment due to periodontitis. Among the most probable of these pathways is progression of localized periodontal inflammation into systemic inflammation. Systemic inflammation, together with other comorbidities, may elicit or add to neuroinflammation that eventually may lead to dementia. For example, increased concentration of inflammatory markers such as C reactive protein and interleukin-6 (IL-6) have been associated with both periodontitis and dementia.

However, well-designed longitudinal studies evaluating changes in inflammation markers in relation to periodontitis and cognition have not been conducted. Therefore, thorough evaluation of inflammation markers at multiple time points during the course of the study, should be undertaken in future studies to clarify the mechanisms by which periodontitis contributes to neurodegeneration. Furthermore, nutritional deficits as a function of tooth loss should be considered in relation to cognitive deterioration, as well as the impact of teeth replacement.

Additionally, the impact of periodontitis on risk of progression of cognitive impairment to dementia should be analyzed. This may facilitate in outlining the timeline, interplay of various confounders and magnitude of impact that periodontitis has on the overall risk and development of dementia.

Both dementia and cognitive impairment are projected to increase significantly in the next few decades. Periodontitis is now widely accepted to be more than a passive determinant of general health, and this review adds to previous literature indicating a possible contribution of periodontitis to the overall risk of dementia and cognitive impairment. Since periodontitis is a preventable disease, preventive strategies for cognitive deterioration incorporating prevention and management of periodontitis could be effectively designed to reduce the risk of cognitive impairment and dementia.

Since periodontitis shares multiple risk factors with dementia, its prevention may have broader effects on the risk of dementia by reducing other common risk factors. More studies investigating various dimensions of the periodontitis-cognition association, such as severity of periodontitis, direct role of periodontal pathogens and possible interplay between different pathological pathways must be carried out to conclusively determine the nature and extent of association between periodontitis and cognitive deterioration.
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