

# Periodontitis: a potential risk factor for Alzheimer's disease



**T. L. Cerajewska,<sup>1</sup> M. Davies<sup>2</sup> and N. X. West<sup>3</sup>** review the available evidence of the potential association between periodontitis and Alzheimer's disease.

## Introduction

The role of periodontitis as a risk factor for multiple systemic diseases is widely accepted and there is growing evidence of an association between periodontitis and sporadic late onset Alzheimer's disease (SLOAD). Recent epidemiologic, microbiologic and inflammatory findings strengthen this association, indicating that periodontal pathogens are possible contributors to neural inflammation and SLOAD. The aim of this article is to present contemporary evidence of this association.

## Alzheimer's disease

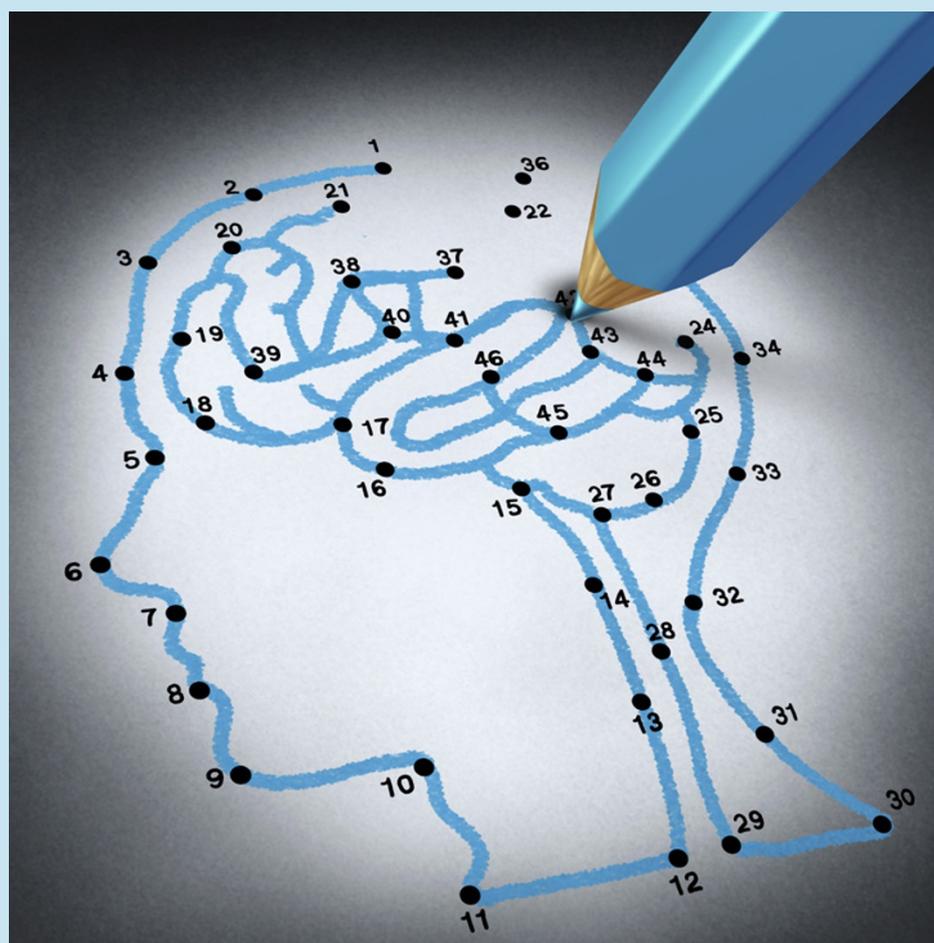
Dementia describes a set of symptoms which includes memory loss, mood changes, problems communicating and difficulty reasoning.<sup>1</sup> Dementia is defined as a reduction in intellectual ability when compared to previous aptitude, which results in impaired function during ordinary daily activities despite unimpaired consciousness.<sup>2</sup>

Alzheimer's disease (AD) is an irreversible progressive neurodegenerative condition and the most common cause of dementia. It is difficult to assess the prevalence of AD due to differing diagnostic criteria, the absence of specific biological markers and the requirement for post-mortem autopsy to establish a definitive diagnosis.<sup>2</sup> However, in 2010 it was estimated that more than 35 million people worldwide were living with AD,<sup>3</sup> and in 2013 it was reported that around 496,000 people in the UK were affected.<sup>1</sup> AD is not necessarily an outcome of ageing,<sup>4</sup> but its incidence approximately doubles every five years from the age of 65 years;<sup>5</sup> the odds of receiving a diagnosis of AD over 85 years of age exceed 1:3.<sup>3</sup> As the ageing population increases the number of people living with AD is set to rise considerably.

## Pathogenesis of Alzheimer's disease

AD is characterised by neuronal loss and the

<sup>1-3</sup>Clinical Trials Group, School of Oral and Dental Science, Lower Maudlin Street, University of Bristol, Bristol, BS1 2LY



**'IN 2010 IT WAS ESTIMATED THAT MORE THAN  
35 MILLION PEOPLE WORLDWIDE WERE  
LIVING WITH ALZHEIMER'S DISEASE'**

presence of senile plaques, which contain  $\beta$ -amyloid ( $A\beta$ ) protein and neurofibrillary tangles of hyper-phosphorylated tau protein.<sup>6</sup> However, it has been shown that plaque accumulation does not correlate with loss of cognitive function,<sup>7</sup> by contrast soluble toxic forms of  $A\beta$  and tau are thought to contribute to the disruption of synaptic function and neurodegeneration.<sup>8,9</sup> Chronic inflammation is also characteristic of AD brains and inflammatory related proteins have been

shown to be involved in the generation of  $A\beta$  and tangle formation.<sup>10</sup>

SLOAD is the most common form of AD, accounting for approximately 98% of all cases.<sup>11</sup> SLOAD has a complex multifactorial aetiology and a polymorphism of the apolipoprotein E4 allele (APOE- $\epsilon$ 4) has been found to be a major risk factor,<sup>12</sup> this gene encourages  $A\beta$  to be deposited in the brain.<sup>13</sup> Although APOE- $\epsilon$ 4 is thought to be the strongest genetic risk factor for SLOAD,<sup>13</sup>

it is only one of 20 loci known to increase the hosts susceptibility to AD.<sup>14</sup> A number of polymorphisms in the genes associated with interleukin-1 (IL-1)<sup>15-19</sup> and tumour necrosis factor alpha (TNF- $\alpha$ ) are believed to alter host susceptibility.<sup>15,20-23</sup>

A number of potentially modifiable risk factors are also thought to have a cumulative detrimental effect on the brain throughout life. These risk factors include infective agents, host immune response, cerebrovascular disease,<sup>24</sup> low cognitive reserve (that is, intelligence, occupation and education),<sup>25</sup> low physical activity levels,<sup>26</sup> alcohol intake,<sup>27</sup> early life depravants, tooth loss,<sup>24</sup> age,<sup>28</sup> head injury,<sup>29</sup> and female gender.<sup>30</sup> Current evidence for individual modifiable risk factors for AD is at best moderate and at worst inconclusive and misleading.<sup>31</sup>

ages.<sup>40,41</sup> Over 38% of US adults aged 30 and over had either moderate or severe periodontitis, however, for adults aged 65 and over this figure increased to 64%.<sup>41</sup>

Periodontitis is a common source of chronic systemic infection.<sup>42-44</sup> The non-keratinised periodontal pocket and junctional epithelium, particularly when ulcerated, can act as an entry portal for bacteria and their endotoxins to enter the systemic circulation.<sup>43,45-47</sup> Presence of such bacteria in the circulatory system causes systemic immunomodulatory effects, which form part of the host response to periodontal pathogens.<sup>41,48,49</sup> In addition to local intraoral effects periodontal disease has a potentially negative impact on general health due to associations with other chronic inflammatory diseases, such as atherosclerotic cardiovascular disease (AVCD),<sup>50-54</sup> diabetes<sup>55</sup>

hinder carer assistance with oral hygiene and result in lower self-esteem and quality of life in those affected.<sup>60</sup> This negative cycle leads to increased periodontal destruction; which has in the past been attributed to poor plaque control. It is also possible that the long-term inflammatory burden on the systemic circulation causes neural degeneration.<sup>65</sup>

The possibility of periodontitis in early and mid-life acting as a precursor to dementia in later life is increasingly being recognised.<sup>51</sup> In such cases the symptoms of dementia were not present in early and mid-life, so dementia impaired oral hygiene would be an unlikely causative factor for the periodontitis observed. Longitudinal data measuring periodontal status, inflammatory markers and cognitive status would be useful,<sup>51</sup> however, such data are in short supply. Many previous studies that have associated periodontitis with AD have not measured periodontal indices or used clinical diagnoses as a measure of the presence and severity of periodontitis as one might expect, instead many relate AD to tooth loss.<sup>24,66-71</sup> While it is likely that some tooth loss is due to periodontitis there are numerous other potential causes of tooth loss, thus an association between periodontitis and AD cannot be reasonably concluded from such studies. For example, patients who have fewer educational experiences and lower cognitive levels are more likely to have extractions<sup>66,72</sup> and also more likely to develop the signs and symptoms of AD.<sup>73</sup> Nevertheless, periodontitis is a potential cause of tooth loss and many studies have associated AD in late-life with tooth loss in early and mid-life.<sup>24,66-71</sup>

Some studies that provide more robust evidence for a causal link between periodontitis and AD have been published. In a longitudinal cohort study, which followed 152 subjects for 20 years, from 50 to 70 years of age, it was found that, for those subjects with fewer than ten missing teeth, greater levels of periodontal inflammation correlated with lower cognitive levels.<sup>60</sup> In another longitudinal ageing cohort study of 144 nuns in Milwaukee it was demonstrated that over time those with APOE- $\epsilon$ 4 and fewer teeth had more rapid rates of cognitive decline than those with neither or either of these risk factors.<sup>71</sup> Moreover, the Veterans Affairs longitudinal cohort study, which followed 597 community dwelling men for 32 years, found that tooth loss, periodontal pockets and progression of alveolar bone loss were associated with impaired cognition particularly in those over 45 years.<sup>74</sup> Further analyses of the third US national health and nutrition survey which included 2,355 people aged 60 years and over, showed associations

## 'POSITIVE CORRELATION BETWEEN ATTAINING PERIODONTAL STABILITY AND DIABETIC CONTROL HAS RECENTLY BEEN RECOGNISED.'

### Periodontal disease

Periodontitis is a progressive destructive condition which affects the gingivae, periodontal ligament and alveolar bone due to chronic multifactorial inflammatory changes in the periodontal tissues as a result of the host response to periodontal pathogens.<sup>32</sup> More than 400 bacterial and viral species have been found to colonise the periodontal pocket.<sup>33</sup> The most virulent bacterial communities tend to contain Gram-negative bacteria capable of tissue invasion. They include *Aggregatibacter actinomycetemcomitans*, *Tanarella forsythia*, *Porphyromonas gingivalis* and *Treponema denticola*.<sup>34,35</sup> Host response to periodontal pathogens can be affected by gene polymorphisms, particularly those that code for IL-1 and TNF- $\alpha$ .<sup>23,36-38</sup> Furthermore, the host response is known to be affected by many lifestyle factors, for example tobacco smoking and stress, which are similarly associated with increased risk of SLOAD.<sup>39</sup> Nutrition and other lifestyle factors are believed to affect gene expression.<sup>23</sup>

In the UK the prevalence of severe periodontitis appears to have increased between 1998 and 2009.<sup>40</sup> UK and US epidemiologic studies indicate that periodontitis affects large numbers of the population and, similar to AD prevalence increases as the population

and cognitive decline.<sup>56</sup> Periodontal disease is recognised as a significant public health concern.<sup>57</sup>

The pathogenesis of periodontitis, ACVD, diabetes and cognitive decline is not fully understood. However, there is an emerging awareness of co-dependent risk and pathogenesis for these diseases and positive correlation between attaining periodontal stability and diabetic control has recently been recognised.<sup>55</sup> Inflammatory and immune responses to infection are thought to provide a connection between these diseases at a fundamental level,<sup>58</sup> indeed, ACVD and diabetes as well as periodontitis are recognised risk factors for SLOAD.<sup>59</sup>

### Epidemiological evidence of an association between Alzheimer's disease and periodontal disease

Oral hygiene is significantly compromised in patients affected by AD because the cognitive processes of learning, attention and memory are progressively damaged. As the neurologic degeneration of AD progresses, daily activities are disrupted by temporal and spatial disorientation and reduced motor skills.<sup>2</sup> Poor oral hygiene and dental morbidity have been correlated with the presence and increased severity of AD.<sup>60-64</sup> The resultant halitosis, discomfort and bleeding when brushing can

between periodontitis and cognitive impairment, and between measures of immunoglobulin to the common periodontal pathogen *Porphyromonas gingivalis* and cognitive test performance.<sup>75</sup> Another epidemiologic study, which included a cohort of 5,138 people aged between 20 and 59 years, revealed that after education and adjustment for other confounding variables, gingival bleeding and loss of periodontal attachment were significantly associated with cognitive impairment.<sup>76</sup>

While epidemiologic evidence suggests periodontal disease may be a risk factor for SLOAD, both chronic periodontitis and SLOAD are multifactorial conditions which share many of the same lifestyle risk factors for example, tobacco smoking and previous education.<sup>40,41,59</sup> Thus, an epidemiologic association between tooth loss/periodontal disease and cognitive impairment does not indicate causation.

#### Plausibility of a potential causal relationship between periodontal disease and Alzheimer's disease: microbial factors

Bacteraemia of oral origin has been recognised since the 1970s.<sup>46,47</sup> It has been speculated that the proliferation and dilation of the periodontal vasculature and ulceration of the periodontal epithelium, seen in chronic periodontitis, provide a larger surface area for the entry of microorganisms into the blood stream compared to healthy gingival tissue.<sup>45</sup> Although this has not been proven beyond doubt, a recent systematic review and meta-analysis determined that plaque accumulation and gingival inflammation significantly increase the prevalence of bacteraemia following tooth brushing.<sup>43</sup> Gingival inflammation has also been significantly associated with the incidence of bacteraemia following scaling and root planing.<sup>44</sup> Thus patients with periodontitis may have a higher risk of developing systemic diseases of oral origin.<sup>77</sup>

The viability of a number of periodontal pathogens in atherosclerotic plaques has recently been recognised,<sup>78,79</sup> and adds credence to the possibility that oral bacteria can reach the brain via the systemic circulation. *Porphyromonas gingivalis*<sup>79,80</sup> and *Treponema denticola*<sup>79,81</sup> have both been implicated in aortic inflammation and atherosclerotic plaque formation with viable bacteria being isolated from both oral and atherosclerotic plaques in animal models. Thus, such pathogens have the potential to linger in the systemic circulation and prolong what was previously thought to be a transient bacteraemia.

It has been speculated that the permeability of the blood-brain barrier increases with age and precedes the development of AD. This has been demonstrated in animal models, where mice that were genetically modified with a mutation in the amyloid precursor protein gene, associated with early onset Alzheimer's disease (EOAD) in humans, were shown to have increased permeability of the blood-brain barrier and increased formation of senile plaques when compared to control mice.<sup>82</sup> The effects became more apparent as the mice aged.

It has also been hypothesised that periodontal pathogens may enter the brain via the peripheral nerve pathways,<sup>83</sup> this being a potential route for the transfer of viruses,

Some of the spirochetes involved were known periodontal pathogens, such as *Treponema denticola*, *Treponema socranskii*, *Treponema pectinovorum* and other oral *Treponema*.

Herpes simplex virus and cytomegalovirus have been isolated from periodontal pockets<sup>95,96</sup> and have also been detected in the brain tissue of older adults with and without AD.<sup>97,98</sup> It has been suggested that latent viruses may be reactivated by immunosuppression, stress or inflammation in the brain and that the APOE-ε4 allele may also affect the reactivation and/or degree of damage caused by viruses within the brain.<sup>99</sup> Indeed the APOE-ε4 allele is likely to make the host more susceptible to a number of environmental risk factors for AD.

## 'PATIENTS WITH PERIODONTITIS MAY HAVE A HIGHER RISK OF DEVELOPING SYSTEMIC DISEASES OF ORAL ORIGIN.'

particularly herpes viruses. The identification of oral *Treponema* in the trigeminal ganglia also supports the neural route.<sup>84</sup> In addition it has been reported by a number of authors that peripheral infections and inflammatory markers can access the brain.<sup>85-87</sup> Furthermore, the circum-ventricular organs are not protected by the blood-brain barrier,<sup>88</sup> and thus could potentially act as an entry portal for bacteria to reach other parts of the brain.<sup>65</sup>

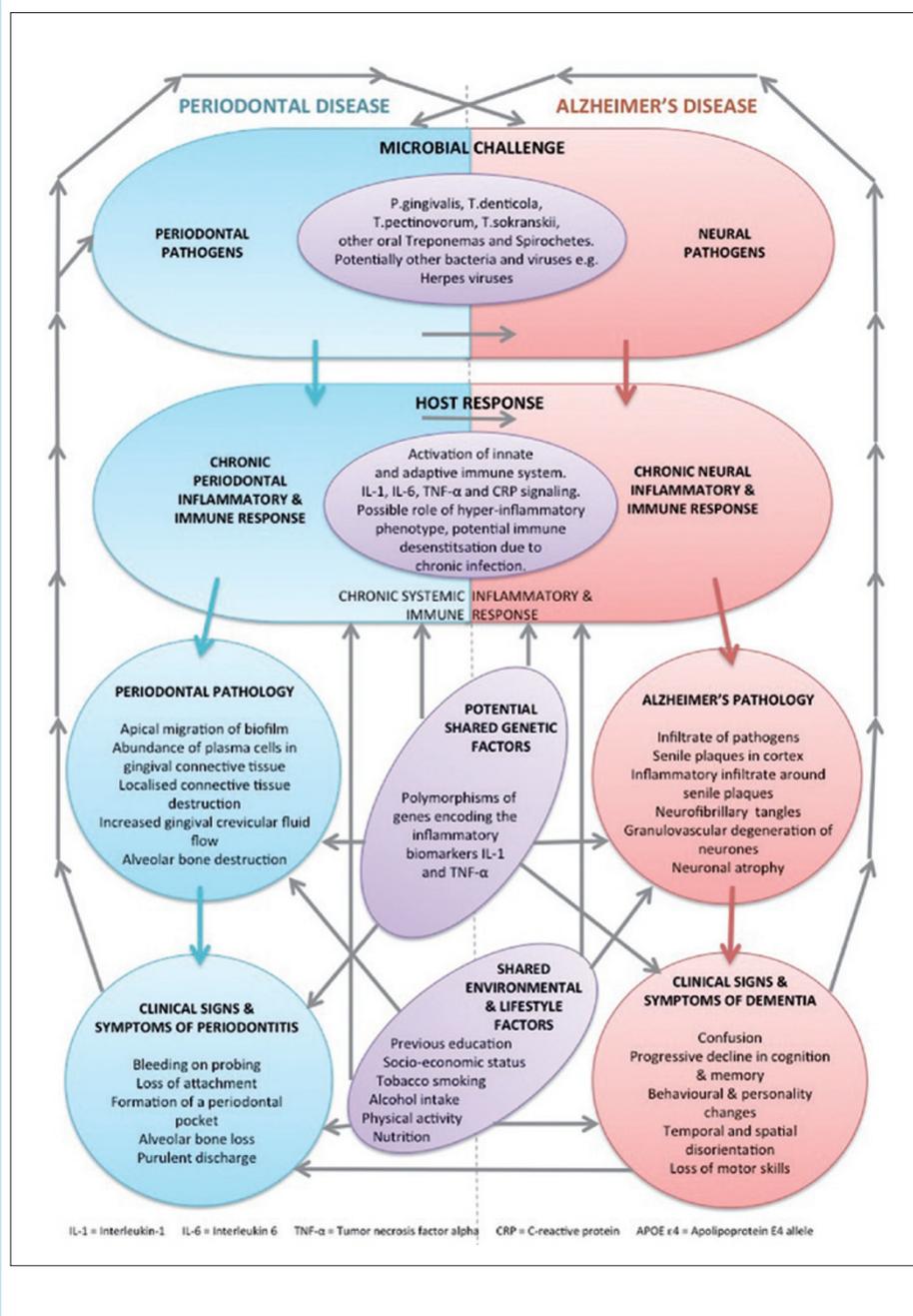
Microorganisms have been isolated more frequently from the brains of AD specimens than age-matched non-AD specimen's post-mortem. *Chlamydophila pneumoniae*<sup>89,90</sup> and the spirochetes *Treponema denticola*<sup>84</sup> and *Borrelia burgdorferi*<sup>91</sup> have all been isolated from AD brain specimens post-mortem, but not always from areas of AD neurodegeneration. Furthermore, *Chlamydia pneumoniae* has been shown to cross the blood-brain barrier in an *in vitro* model<sup>92</sup> and to be capable of inducing amyloid plaque formation in an animal model.<sup>93</sup> More recently, lipopolysaccharide from *Porphyromonas gingivalis* has been shown capable of crossing the blood-brain barrier in AD brain samples but not in non-AD control brain samples post-mortem.<sup>94</sup> A seminal article which assessed the available evidence for an association between spirochetes in the brain and Alzheimer's disease against Koch's and Hill's postulates found a causal relationship was probable.<sup>73</sup>

#### Inflammatory mechanisms linking periodontal disease and Alzheimer's disease

Fundamental to the inflammatory hypothesis of AD is inflammation in the brain, which once begun continues and causes neurodegeneration.<sup>100</sup> This is believed to occur due to microbial stimulation of the immune response, which causes glial cells to release the Aβ and hyperphosphorylated tau proteins, found in senile plaques and neurofibrillary tangles, in a positively perpetuating cycle.<sup>83</sup> Chronic inflammation is not thought to be the primary cause of AD, rather a secondary phenomenon. However, reducing cerebral inflammation may slow the progress and delay the onset of AD.<sup>101</sup> Chronic periodontitis has been shown to result in sustained and increased levels of inflammatory products in the circulation.<sup>102</sup> Individuals vary in their susceptibility to infection, partly due to the components within the biofilm and partly due to their particular genotype.<sup>51</sup> A hyper-inflammatory phenotype has been associated with periodontitis,<sup>103,104</sup> that causes some individuals to have exaggerated inflammatory responses to pathogens.

Inflammatory biomarkers include cytokines (intercellular signalling molecules that have an immuno-modulatory effect) such as IL-1, interleukin 6 and TNF-α, as well as acute phase proteins including C-reactive protein. Inflammatory cytokines produced by the periodontal tissues during

**Fig. 1** Shared features for periodontitis and Alzheimer's disease pathogenesis



periodontitis can enter into the blood stream,<sup>105–107</sup> and have been implicated both in periodontitis<sup>23,51,102,108–111</sup> and in the neurological changes of AD.<sup>23,51,112–122</sup> It could be that AD and periodontitis share the same or similar hyper-inflammatory phenotypes, that when activated by certain environmental factors have a detrimental effect on host periodontal and neural tissue.

It remains uncertain whether systemic inflammation precedes AD, so it is also possible that the peripheral inflammatory response, mounted against periodontal pathogens or the pathogens themselves could induce or increase neural inflammation

and thus contribute to AD onset and progression. Regardless of the cause, systemic inflammation has been shown to predict dementia.<sup>51,116,118</sup>

A $\beta$  aggregation, central to the amyloid cascade hypothesis of AD, has been shown to be modulated in response to a number of environmental stressors, to act as ligand for a number of receptors and molecules which have been transported across the blood-brain barrier and to induce a number of pro-inflammatory activities. A $\beta$  has been shown to be active against eight clinically relevant microorganisms *in vitro*.<sup>123</sup> It was proposed, therefore, that A $\beta$  is an antimicrobial

peptide acting as an effector molecule of innate immunity. The same study found that temporal lobe samples from the AD brains contained significantly higher antimicrobial activity than the brains of age-matched, non-AD subjects.

Stimulation of the innate immune system by persistent sub-acute infection of the brain with bacteria or viruses may trigger an amyloid cascade leading to A $\beta$  generation and deposition.<sup>123</sup> Genetic factors could also influence A $\beta$  production and clearance. While the genes associated with EOAD are believed to cause A $\beta$  accumulation without a trigger from the innate immune system,<sup>124</sup> individuals with APOE- $\epsilon$ 4 gene associated with SLOAD may be more susceptible to cerebral infection.<sup>125</sup> Transient cerebral infection or non-infective insult to the brain may lead to a persistent self-perpetuating innate immune response; this could be the result of traumatic brain injury,<sup>126</sup> stroke,<sup>127</sup> or gaseous anaesthetic agents.<sup>128</sup>

### Requirement for future clinical intervention studies

Predictions of a global AD epidemic estimate that the prevalence is set to quadruple from 2006 to 2050.<sup>129</sup> Without a cure for AD and in the face of an epidemic the cost of dementia to the global economy is set to rise significantly from the 2010 estimate of £604 billion.<sup>130</sup> It has been estimated that the annual cost for institutionalised dementia care in the UK will rise from £5.1 million in 2002 to £16.7 million in 2031.<sup>131</sup> According to expert consensus opinion the disabling effects of dementia are surpassed only by terminal cancer and spinal cord injury,<sup>132</sup> and place a vast physical, psychological and economic strain on those affected and their carers, friends and family.<sup>133</sup>

While available drug treatments for AD, that is cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, can provide symptomatic benefits, they do not alter the progressive neuro-degeneration or end-stage outcome of AD.<sup>134,135</sup> In 2010 an independent expert consensus report concluded that recommendations for the prevention of AD and cognitive decline could not be made due to a lack of robust evidence.<sup>31</sup> This highlights the need for further research into potential modifiable risk factors for AD including periodontitis.

Periodontal therapy has been shown to reduce peripheral infection and the systemic inflammatory biomarkers for periodontitis and AD.<sup>136,137</sup> Further research is required to determine whether reducing the systemic bacterial and inflammatory load through effective periodontal therapy may delay the

onset and progression of Alzheimer's disease.

If effective periodontal therapy could delay the onset and progression of AD by one year it has been predicted that there could be almost 9.2 million fewer cases of AD by 2050, with much of the decline ascribed to those who require the most costly care.<sup>129</sup> Such an effect would also be likely to improve patients and their carers' quality of life.

### Potential further research

As it remains to be determined whether periodontitis is a risk factor for Alzheimer's disease and whether effective treatment of periodontitis will delay the onset and progression of SLOAD further research studies are indicated, these include:

- Longitudinal epidemiologic cohort studies that follow a population and measure their periodontal and cognitive status from middle to old age to confirm a correlation
  - Post-mortem analysis to compare levels of periodontal pathogens in brain tissue from patients with AD and healthy controls. Identification of new periodontal pathogens not yet associated with Alzheimer's disease and determination of their micro-anatomical association to the histopathological hallmarks of AD
  - *In vitro* or mammalian model studies to determine how periodontal pathogens enter the brain, their ability to form biofilms in the brain once there and the mechanisms by which they and the immune and inflammatory response could induce the pathological changes associated with AD
  - Studies to determine whether the genetic polymorphisms associated with SLOAD are associated with periodontitis and vice versa
  - Pilot clinical and quality of life studies to determine whether it is feasible to effectively treat periodontal disease in those who suffer from AD
  - Clinical trials to measure the impact of periodontal treatment on inflammatory biomarkers, presentation, progression and quality of life of those who suffer from AD.
- Such research will be particularly challenging due to the multifactorial aetiology and chronic nature of periodontitis and AD.

The specific needs and disabilities of those who suffer from AD will also pose unique challenges. To validate findings research will require collaboration between experts from scientific, medical and dental disciplines, independent and multi-centre investigations, adequate funding support and large sample sizes for clinical intervention trials with careful statistical analysis to determine the effects of potential confounding variables. It is therefore likely that progress in this field will be gradual.

### Conclusion

Current literature suggests an association and shared pathogenesis between periodontitis and AD, which has been summarised in Figure 1. The mechanisms of this association

are not fully understood. Therefore, further research is required to prove and determine the *raison d'être* for this association. Several potentially coexistent theories are proposed:

- The direct invasion of periodontal pathogens and/or their virulence factors into brain tissue is implicated in the pathogenesis of AD
- Chronic exposure to periodontal pathogens and their endotoxins result in modification of the systemic inflammatory mediators, which are implicated in the pathogenesis of AD
- Periodontitis and AD may share a common underlying cause due to expression of underlying hyper-inflammatory phenotypes
- The effects of periodontal pathogens on the systemic circulation are implicated in the formation of atherosclerotic plaques and therefore, AD is an outcome of inflammatory changes to vessel walls and reduced blood flow to the brain
- AD and periodontitis share risk factors and similar, but non-contributory, inflammatory pathogenesis
- The effects of AD have a negative effect on plaque control, which has a detrimental effect on periodontal health.

1. Alzheimer's Society. *What is Alzheimer's disease?* London: Alzheimer's Society, 2013.
2. Ghezzi E M, Ship J A. Dementia and oral health. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*

- 2000; **89**: 2–5.
3. Querfurth H W, LaFerla F M. Alzheimer's disease. *New Engl J Med* 2010; **362**: 329–344.
4. den Dunnen W F, Brouwer W H, Bijlard E *et al*. No disease in the brain of a 115-year-old woman. *Neurobiol Aging* 2008; **29**: 1127–1132.
5. Hirtz D, Thurman D J, Gwinn-Hardy K, Mohamed M, Chaudhuri A R, Zalutsky R. How common are the «common» neurologic disorders? *Neurology* 2007; **68**: 326–337.
6. Selkoe D J. Alzheimer's disease. *Cold Spring Harbor Perspectives Biology* 2011; **3**: 1–16.
7. Ingelsson M, Fukumoto H, Newell K L *et al*. Early Abeta accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. *Neurology* 2004; **62**: 925–931.
8. Lesne S E. Breaking the Code of Amyloid-beta Oligomers. *Int J Cell Biol* 2013; 950783.
9. Spiers-Jones T L, Hyman B T. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron* 2014; **82**: 756–771.
10. Eikelenboom P, Hoozemans J J, Veerhuis R, van Exel E, Rozemuller AJ, van Gool WA. Whether, when and how chronic inflammation increases the risk of developing late-onset Alzheimer's disease. *Alzheimers Res Ther* 2012; **4**: 15.
11. Noble J M, Scarmeas N, Papapanou P N. Poor oral health as a chronic, potentially modifiable dementia risk factor: review of the literature. *Curr Neurol Neurosci Rep* 2013; **13**: 384.
12. Corder E H, Saunders A M, Strittmatter W J *et al*. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; **261**: 921–923.
13. Potter H, Wisniewski T. Apolipoprotein e: essential catalyst of the Alzheimer amyloid cascade. *Int J Alzheimers Dis* 2012; 489428.
14. Lambert J C, Ibrahim-Verbaas C A, Harold D, Naj A C *et al*. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* 2013; **45**: 1452–1458.
15. McGeer P L, McGeer E G. Polymorphisms in inflammatory genes and the risk of Alzheimer disease. *Arch Neurol* 2001; **58**: 1790–1792.
16. Yuan H, Xia Q, Ge P, Wu S. Genetic polymorphism of interleukin 1beta511C/T and susceptibility to sporadic Alzheimer's disease: a meta-analysis. *Mol Biol Rep* 2013; **40**: 1827–1834.
17. Di Bona D, Plaia A, Vasto S *et al*. Association between the interleukin-1beta polymorphisms and Alzheimer's disease: a systematic review and meta-analysis. *Brain Res Rev* 2008; **59**: 155–163.
18. Zhu X C, Tan L, Jiang T, Tan M S, Zhang W, Yu J T. Association of IL-12A and IL-12B polymorphisms with Alzheimer's disease susceptibility in a Han Chinese population. *J Neuroimmunol* 2014; **274**: 180–184.
19. Payao S L, Goncalves G M, de Labio R W *et al*. Association of interleukin 1beta polymorphisms and haplotypes with Alzheimer's disease. *J Neuroimmunol* 2012; **247**: 59–62.
20. Wang B, Zhou S, Yang Z *et al*. Genetic analysis of tumor necrosis factor-alpha (TNF-alpha) G-308A and Saitohin Q7R polymorphisms with Alzheimer's disease. *J Neurol Sci* 2008; **270**: 148–151.
21. Di Bona D, Candore G, Franceschi C *et al*. Systematic review by meta-analyses on the possible role of TNF-alpha polymorphisms in association with Alzheimer's disease. *Brain Res Rev* 2009; **61**: 60–68.
22. Lio D, Annoni G, Licastro F *et al*. Tumor necrosis factoralpha308A/G polymorphism is associated with age at onset of Alzheimer's disease. *Mech Ageing Develop* 2006; **127**: 567–571.
23. Kornman K S. Interleukin 1 genetics, inflammatory mechanisms, and nutrigenetic

- opportunities to modulate diseases of aging. *Am J Clin Nutr* 2006; **83**: 475S-483S.
24. Gatz M, Mortimer J A, Fratiglioni L *et al*. Potentially modifiable risk factors for dementia in identical twins. *Alzheimers Dement* 2006; **2**: 110-117.
  25. Valenzuela M J, Sachdev P. Brain reserve and dementia: a systematic review. *Psychol Med* 2006; **36**: 441-454.
  26. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med* 2009; **39**: 3-11.
  27. Anstey K J, Mack H A, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *Am J Geriatr Psychiatry* 2009; **17**: 542-555.
  28. Ferri C P, Prince M, Brayne C *et al*. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005; **366**: 2112-2117.
  29. Sundstrom A, Nilsson L G, Cruts M, Adolfsen R, Van Broeckhoven C, Nyberg L. Increased risk of dementia following mild head injury for carriers but not for non-carriers of the APOE epsilon4 allele. *Int Psychogeriatrics* 2007; **19**: 159-165.
  30. Kocaeli H, Yaltrik M, Yargic L I, Ozbas H. Alzheimer's disease and dental management. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**: 521-524.
  31. Anon. Alzheimer's disease prevention: a reality check. *Lancet Neurol* 2010; **9**: 643.
  32. American Association of Periodontology. *Glossary of periodontal terms*. Chicago, Illinois, USA: American Academy of Periodontology, 2001.
  33. Paster B J, Olsen I, Aas J A, Dewhirst F E. The breadth of bacterial diversity in the human periodontal pocket and other oral sites. *Periodontol 2000* 2006; **42**: 80-87.
  34. Socransky S S, Haffajee A D, Cugini M A, Smith C, Kent R L Jr. Microbial complexes in subgingival plaque. *J Clin Periodontol* 1998; **25**: 134-144.
  35. Socransky S S, Haffajee A D. Dental biofilms: difficult therapeutic targets. *Periodontol 2000* 2002; **28**: 12-55.
  36. Kornman K S, Crane A, Wang H Y *et al*. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol* 1997; **24**: 72-77.
  37. Ding C, Ji X, Chen X, Xu Y, Zhong L. TNF-alpha gene promoter polymorphisms contribute to periodontitis susceptibility: evidence from 46 studies. *J Clin Periodontol* 2014; **41**: 748-759.
  38. Soga Y, Nishimura F, Ohyama H, Maeda H, Takashiba S, Murayama Y. Tumor necrosis factor-alpha gene (TNF-alpha)-1031/-863,-857 single-nucleotide polymorphisms (SNPs) are associated with severe adult periodontitis in Japanese. *J Clin Periodontol* 2003; **30**: 524-531.
  39. Singhrao S K, Harding A, Simmons T, Robinson S, Kesavalu L, Crean S. Oral inflammation, tooth loss, risk factors, and association with progression of Alzheimer's disease. *J Alzheimers Dis* 2014; **42**: 723-737.
  40. White D A, Tsakos G, Pitts N B *et al*. Adult Dental Health Survey 2009: common oral health conditions and their impact on the population. *Br Dent J* 2012; **213**: 567-572.
  41. Eke P I, Dye B A, Wei L, Thornton-Evans G O, Genco R J, Cdc Periodontal Disease Surveillance workgroup: James Beck G D R P. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *J Dent Res* 2012; **91**: 914-920.
  42. Garcia R I, Henshaw M M, Krall E A. Relationship between periodontal disease and systemic health. *Periodontol 2000* 2001; **25**: 21-36.
  43. Tomas I, Diz P, Tobias A, Scully C, Donos N. Periodontal health status and bacteraemia from daily oral activities: systematic review/meta-analysis. *J Clin Periodontol* 2012; **39**: 213-228.
  44. Zhang W, Daly C G, Mitchell D, Curtis B. Incidence and magnitude of bacteraemia caused by flossing and by scaling and root planing. *J Clin Periodontol* 2013; **40**: 41-52.
  45. Parahitiyawa N B, Jin L J, Leung W K, Yam W C, Samaranyake L P. Microbiology of odontogenic bacteraemia: beyond endocarditis. *Clin Microbiol Rev* 2009; **22**: 46-64.
  46. Silver J G, Martin A W, McBride B C. Experimental transient bacteraemias in human subjects with varying degrees of plaque accumulation and gingival inflammation. *J Clin Periodontol* 1977; **4**: 92-99.
  47. Sconyers J R, Crawford J J, Moriarty J D. Relationship of bacteraemia to tooth-brushing in patients with periodontitis. *J Am Dent Assoc* 1973; **87**: 616-622.
  48. Page R C, Schroeder H E. Pathogenesis of inflammatory periodontal disease. A summary of current work. *Lab Invest* 1976; **34**: 235-249.
  49. Seymour G J, Gemmell E, Reinhardt R A, Eastcott J, Taubman M A. Immunopathogenesis of chronic inflammatory periodontal disease: cellular and molecular mechanisms. *J Periodontol Res* 1993; **28**: 478-486.
  50. Tonetti M S, Van Dyke TE, working group 1 of the joint EFPAAp. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol* 2013; **84**: S24-29.
  51. Watts A, Crimmins E M, Gatz M. Inflammation as a potential mediator for the association between periodontal disease and Alzheimer's disease. *Neuropsychiatr Dis Treat* 2008; **4**: 865-876.
  52. DeStefano F, Anda R F, Kahn H S, Williamson D F, Russell C M. Dental disease and risk of coronary heart disease and mortality. *BMJ* 1993; **306**: 688-691.
  53. Arbes S J, Jr., Slade G D, Beck J D. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. *J Dent Res* 1999; **78**: 1777-1782.
  54. Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. *J Periodontol* 2013; **84**: S70-84.
  55. Chapple I L, Genco R, Working group 2 of joint EFPAAp. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on periodontitis and systemic diseases. *J Clin Periodontol* 2013; **40**: S106-112.
  56. Linden G J, Lyons A, Scannapieco F A. Periodontal systemic associations: review of the evidence. *J Periodontol* 2013; **84**: S8-S19.
  57. Chapple I L, Wilson N H. Manifesto for a paradigm shift: periodontal health for a better life. *Br Dent J* 2014; **216**: 159-162.
  58. Van Dyke T E, van Winkelhoff A J. Infection and inflammatory mechanisms. *J Periodontol* 2013; **84**: S1-7.
  59. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet* 2011; **377**: 1019-1031.
  60. Cicciu M, Maticena G, Signorino F, Brugaletta A, Cicciu A, Bramanti E. Relationship between oral health and its impact on the quality life of Alzheimer's disease patients: a supportive care trial. *Int J Clin Exp Med* 2013; **6**: 766-772.
  61. Ribeiro G R, Costa J L, Ambrosano G M, Garcia R C. Oral health of the elderly with Alzheimer's disease. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **114**: 338-343.
  62. Hugo F N, Hilgert J B, Bertuzzi D, Padilha D M, De Marchi R J. Oral health behaviour and socio-demographic profile of subjects with Alzheimer's disease as reported by their family caregivers. *Gerodontology* 2007; **24**: 36-40.
  63. Hatipoglu M G, Kabay S C, Guven G. The clinical evaluation of the oral status in Alzheimer-type dementia patients. *Gerodontology* 2011; **28**: 302-306.
  64. Syrjala A M, Ylostalo P, Ruoppi P *et al*. Dementia and oral health among subjects aged 75 years or older. *Gerodontology* 2012; **29**: 36-42.
  65. Poole S, Singhrao S. K, Crean, St. J. Emerging evidence for an association between periodontitis and the development of Alzheimer's disease. *Faculty Dent J* 2014; **5**: 39-42.
  66. Starr J M, Hall R J, Macintyre S, Deary I J, Whalley L J. Predictors and correlates of edentulism in the healthy old people in Edinburgh (HOPE) study. *Gerodontology* 2008; **25**: 199-204.
  67. Kim J M, Stewart R, Prince M *et al*. Dental health, nutritional status and recent-onset dementia in a Korean community population. *Int J Geriatr Psychiatry* 2007; **22**: 850-855.
  68. Grabe H J, Schwahn C, Volzke H *et al*. Tooth loss and cognitive impairment. *J Clin Periodontol* 2009; **36**: 550-557.
  69. Arrive E, Letenneur L, Matharan F *et al*. Oral health condition of French elderly and risk of dementia: a longitudinal cohort study. *Comm Dent Oral Epidemiol* 2012; **40**: 230-238.
  70. Paganini-Hill A, White S C, Atchison K A. Dentition, dental health habits, and dementia: the Leisure World Cohort study. *J Am Geriatr Soc* 2012; **60**: 1556-1563.
  71. Stein P S, Kryscio R J, Desrosiers M, Donegan S J, Gibbs M B. Tooth loss, apolipoprotein E, and decline in delayed word recall. *J Dent Res* 2010; **89**: 473-477.
  72. Treasure E, Kelly M, Nuttall N, Nunn J, Bradnock G, White D. Factors associated with oral health: a multivariate analysis of results from the 1998 Adult Dental Health survey. *Br Dent J* 2001; **190**: 60-68.
  73. Kamer A R, Morse D E, Holm-Pedersen P, Mortensen E L, Avlund K. Periodontal inflammation in relation to cognitive function in an older adult Danish population. *J Alzheimers Dis* 2012; **28**: 613-624.
  74. Kaye E K, Valencia A, Baba N, Spiro A 3rd, Dietrich T, Garcia R I. Tooth loss and periodontal disease predict poor cognitive function in older men. *J Am Geriatr Soc* 2010; **58**: 713-718.
  75. Noble J M, Borrell L N, Papananou P N, Elkind M S, Scarmeas N, Wright C B. Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III. *J Neurol Neurosurg Psych* 2009; **80**: 1206-1211.
  76. Stewart R, Sabbah W, Tsakos G, D'Aiuto F, Watt R G. Oral health and cognitive function in the Third National Health and Nutrition Examination Survey (NHANES III). *Psychosom Med* 2008; **70**: 936-941.
  77. Olsen I. Update on bacteraemia related to dental procedures. *Transfus Apher Sci* 2008; **39**: 173-178.
  78. Reyes L, Herrera D, Kozarov E, Rolda S, Progulsk-Fox A. Periodontal bacterial invasion and infection: contribution to atherosclerotic pathology. *J Periodontol* 2013; **84**: S30-50.
  79. Rivera M F, Lee J Y, Aneja M *et al*. Polymicrobial infection with major periodontal pathogens induced periodontal disease and aortic atherosclerosis in hyperlipidemic ApoE(null) mice. *PLoS one* 2013; **8**: e57178.
  80. Velsko I M, Chukkappalli S S, Rivera M F *et al*. Active Invasion of Oral and Aortic Tissues by Porphyromonas gingivalis in Mice Causally Links Periodontitis and Atherosclerosis. *PLoS one* 2014; **9**: e97811.

81. Chukkapalli S S, Rivera M F, Velsko I M *et al.* Invasion of oral and aortic tissues by oral spirochete *Treponema denticola* in ApoE(-/-) mice causally links periodontal disease and atherosclerosis. *Infection Immun* 2014; **82**: 1959–1967.
82. Ujiie M, Dickstein D L, Carlow D A, Jefferies W A. Blood-brain barrier permeability precedes senile plaque formation in an Alzheimer disease model. *Microcirculation* 2003; **10**: 463–470.
83. Kamer A R, Craig R G, Dasanayake A P, Brys M, Glodzik-Sobanska L, de Leon M J. Inflammation and Alzheimer's disease: possible role of periodontal diseases. *Alzheimers Dement* 2008; **4**: 242–250.
84. Riviere G R, Riviere K H, Smith K S. Molecular and immunological evidence of oral *Treponema* in the human brain and their association with Alzheimer's disease. *Oral Microbiol Immunol* 2002; **17**: 113–118.
85. Branton W G, Ellestad K K, Maingat F *et al.* Brain microbial populations in HIV/AIDS: alpha-proteobacteria predominate independent of host immune status. *PLoS One* 2013; **8**: e54673.
86. Miklossy J. Alzheimer's disease neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. *J Neuroinflammation* 2011; **8**: 90.
87. Rivest S. Regulation of innate immune responses in the brain. *Nat Rev Immunol* 2009; **9**: 429–439.
88. Fry M, Ferguson A V. The sensory circumventricular organs: brain targets for circulating signals controlling ingestive behavior. *Physiol Behav* 2007; **91**: 413–423.
89. Hammond C J, Hallock L R, Howanski R J, Appelt D M, Little C S, Balin B J. Immunohistological detection of *Chlamydia pneumoniae* in the Alzheimer's disease brain. *BMC Neurosci* 2010; **11**: 121.
90. Balin B J, Gerard H C, Arking E J *et al.* Identification and localization of *Chlamydia pneumoniae* in the Alzheimer's brain. *Med Microbiol Immunol* 1998; **187**: 23–42.
91. Miklossy J, Kis A, Radenovic A *et al.* Beta-amyloid deposition and Alzheimer's type changes induced by *Borrelia spirochetes*. *Neurobiol Aging* 2006; **27**: 228–236.
92. MacIntyre A, Abramov R, Hammond C J *et al.* *Chlamydia pneumoniae* infection promotes the transmigration of monocytes through human brain endothelial cells. *J Neurosci Res* 2003; **71**: 740–750.
93. Little C S, Hammond C J, MacIntyre A, Balin B J, Appelt D M. *Chlamydia pneumoniae* induces Alzheimer-like amyloid plaques in brains of BALB/c mice. *Neurobiol Aging* 2004; **25**: 419–429.
94. Poole S, Singhrao S K, Kesavalu L, Curtis M A, Crean S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. *J Alzheimers Dis* 2013; **36**: 665–677.
95. Parra B, Slots J. Detection of human viruses in periodontal pockets using polymerase chain reaction. *Oral Microbiol Immunol* 1996; **11**: 289–293.
96. Contreras A, Zadeh H H, Nowzari H, Slots J. Herpesvirus infection of inflammatory cells in human periodontitis. *Oral Microbiol Immunol* 1999; **14**: 206–212.
97. Aiello A E, Haan M, Blythe L, Moore K, Gonzalez J M, Jagust W. The influence of latent viral infection on rate of cognitive decline over 4 years. *J Am Geriatr Soc* 2006; **54**: 1046–1054.
98. Itzhaki R F, Lin W R, Shang D, Wilcock G K, Faragher B, Jamieson G A. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet* 1997; **349**: 241–244.
99. Itzhaki R F, Wozniak M A. Herpes simplex virus type 1, apolipoprotein E, and cholesterol: a dangerous liaison in Alzheimer's disease and other disorders. *Prog Lipid Res* 2006; **45**: 73–90.
100. Akiyama H, Barger S, Barnum S *et al.* Inflammation and Alzheimer's disease. *Neurobiol Aging* 2000; **21**: 383–421.
101. McGeer P L, McGeer E G. Inflammation of the brain in Alzheimer's disease: implications for therapy. *J Leukocyte Biol* 1999; **65**: 409–415.
102. Loos B G. Systemic markers of inflammation in periodontitis. *J Periodontol* 2005; **76**: 2106–2115.
103. Kornman K S, Pankow J, Offenbacher S, Beck J, di Giovine F, Duff G W. Interleukin-1 genotypes and the association between periodontitis and cardiovascular disease. *J Periodontol Res* 1999; **34**: 353–357.
104. Beck J, Garcia R, Heiss G, Vokonas P S, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol* 1996; **67**: 1123–1137.
105. Page R C. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. *Ann Periodontol* 1998; **3**: 108–120.
106. Offenbacher S. Periodontal diseases: pathogenesis. *Ann Periodontol* 1996; **1**: 821–878.
107. Amar S, Han X. The impact of periodontal infection on systemic diseases. *Int Med J Exp Clin Res* 2003; **9**: RA291–299.
108. Galbraith G M, Hendley T M, Sanders J J, Palesch Y, Pandey J P. Polymorphic cytokine genotypes as markers of disease severity in adult periodontitis. *J Clin Periodontol* 1999; **26**: 705–709.
109. Bretz W A, Weyant R J, Corby P M *et al.* Systemic inflammatory markers, periodontal diseases, and periodontal infections in an elderly population. *J Am Geriatr Soc* 2005; **53**: 1532–1537.
110. D'Aiuto F, Parkar M, Andreou G *et al.* Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res* 2004; **83**: 156–160.
111. Masada M P, Persson R, Kenney J S, Lee S W, Page R C, Allison A C. Measurement of interleukin-1 alpha and 1 beta in gingival crevicular fluid: implications for the pathogenesis of periodontal disease. *J Periodontol Res* 1990; **25**: 156–163.
112. Kronfol Z, Remick D G. Cytokines and the brain: implications for clinical psychiatry. *Am J Psychiatry* 2000; **157**: 683–694.
113. Strauss S, Bauer J, Ganter U, Jonas U, Berger M, Volk B. Detection of interleukin-6 and alpha 2-macroglobulin immunoreactivity in cortex and hippocampus of Alzheimer's disease patients. *Lab Invest* 1992; **66**: 223–230.
114. Cox G J. Interleukin-6. In Remick DFJ (ed) *Cytokines in health and disease*. 2nd ed. New York: Marcel Dekker, 1997.
115. Rainero I, Bo M, Ferrero M, Valfre W, Vaula G, Pinessi L. Association between the interleukin-1alpha gene and Alzheimer's disease: a meta-analysis. *Neurobiol Aging* 2004; **25**: 1293–1298.
116. Holmes C, El-Okli M, Williams A L, Cunningham C, Wilcockson D, Perry V H. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2003; **74**: 788–789.
117. Grammas P, Ovasse R. Inflammatory factors are elevated in brain microvessels in Alzheimer's disease. *Neurobiol Aging* 2001; **22**: 837–842.
118. Engelhart M J, Geerlings M I, Meijer J *et al.* Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. *Arch Neurol* 2004; **61**: 668–672.
119. Marx F, Blasko I, Pavelka M, Grubeck-Loebenstien B. The possible role of the immune system in Alzheimer's disease. *Exp Gerontol* 1998; **33**: 871–881.
120. Heneka M T, O'Banion M K. Inflammatory processes in Alzheimer's disease. *J Neuroimmunol* 2007; **184**: 69–91.
121. Perry V H. The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. *Brain Behav Immun* 2004; **18**: 407–413.
122. McCusker S M, Curran M D, Dynan K B *et al.* Association between polymorphism in regulatory region of gene encoding tumour necrosis factor alpha and risk of Alzheimer's disease and vascular dementia: a case-control study. *Lancet* 2001; **357**: 436–439.
123. Soscia S J, Kirby J E, Washicosky K J *et al.* The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. *PLoS One* 2010; **5**: e9505.
124. Tanzi R E, Kovacs D M, Kim T W, Moir R D, Guenette S Y, Wasco W. The gene defects responsible for familial Alzheimer's disease. *Neurobiol Dis* 1996; **3**: 159–168.
125. Urosevic N, Martins R N. Infection and Alzheimer's disease: the APOE epsilon4 connection and lipid metabolism. *J Alzheimers Dis* 2008; **13**: 421–435.
126. Roberts G W, Gentleman S M, Lynch A, Graham D I. beta A4 amyloid protein deposition in brain after head trauma. *Lancet* 1991; **338**: 1422–1423.
127. Tesco G, Koh Y H, Kang E L *et al.* Depletion of GGA3 stabilizes BACE and enhances beta-secretase activity. *Neuron* 2007; **54**: 721–737.
128. Xie Z, Dong Y, Maeda U *et al.* Isoflurane-induced apoptosis: a potential pathogenic link between delirium and dementia. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 1300–1306.
129. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi H M. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 2007; **3**: 186–191.
130. Wimo A, Jonsson L, Bond J, Prince M, Winblad B. Alzheimer Disease I. The worldwide economic impact of dementia 2010. *Alzheimers Dement* 2013; **9**: 1–11 e3.
131. Comas-Herrera A, Wittenberg R, Pickard L, Knapp M. Cognitive impairment in older people: future demand for long-term care services and the associated costs. *Int J Geriatr Psychiatry* 2007; **22**: 1037–1045.
132. World Health Organisation. *World Health Report 2003 - Shaping the future*. Geneva: World Health Organisation, 2003.
133. Schneider J, Murray J, Banerjee S, Mann A. EURO CARE: a cross-national study of co-resident spouse carers for people with Alzheimer's disease: IFactors associated with carer burden. *Int J Geriatr Psychiatry* 1999; **14**: 651–661.
134. Turner L N, Balasubramaniam R, Hersh E V, Stoopler E T. Drug therapy in Alzheimer disease: an update for the oral health care provider. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; **106**: 467–476.
135. Corbett A, Williams G, Ballard C. Drug repositioning: an opportunity to develop novel treatments for Alzheimer's disease. *Pharmaceuticals* 2013; **6**: 1304–1321.
136. Vidal F, Figueredo C M, Cordovil I, Fischer R G. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension. *J Periodontol* 2009; **80**: 786–791.
137. Bresolin A C, Pronsatti M M, Pasqualotto L N *et al.* Effectiveness of periodontal treatment on the improvement of inflammatory markers in children. *Arch Oral Biol* 2014; **59**: 639–644.

bdjteam201662