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Impact of Oral Health on Cognitive Functioning, Decline and Impairment Among Older Adults in England

Mohammed Ibrahim H Alsaif

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Department of Epidemiology and Public Health

University College London

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Declaration of Authorship

I, Mohammed Alsaif, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in this thesis.

Signature: ……

(Mohammed Alsaif)

Date: ……

Abstract

Background: Several studies have assessed the association between oral health and cognition in the elderly, although very few studies have investigated the longitudinal association in England. Different theories have been reported in the literature explaining the potential pathways between oral health and cognitive impairment, including inflammatory and nutritional factors. Additionally, social factors are a significant risk factor for cognitive impairment and are also highly correlated with oral health.

Aim: This thesis aimed to examine the association between various oral health measures with cognitive functioning, change of cognitive functioning over time, and cognitive impairment in a nationally representative sample of older English adults. Additionally, the inflammatory, nutritional and social pathways were assessed.

Methods: Secondary data from wave 3 (2006-07) to wave 8 (2016-17) of the English Longitudinal Study of Ageing (ELSA) were analysed. Three oral health measures were examined at baseline (wave 3) including self-reported oral health, oral impacts and edentulism. Cognitive functioning outcomes examined were memory using the word recall test and executive function using the animal naming test. Cognitive impairment was assessed at the follow-up wave 8 using the modified Telephone Interview for Cognitive Status (mTICS). Linear regression was used to assess the association with cognitive functioning cross-sectionally and longitudinally, linear mixed-effects models were used to assess the association with the change of cognitive functioning over time, and time-lag logistic regression models were used to assess the association with the subsequent cognitive impairment. Finally, several Structural Equation Models (SEM) were used to analyse the potential pathways of the association between oral health and cognitive impairment.

Results: This thesis showed that edentulism significantly predicted lower memory and executive function; while self-reported oral health predicted lower memory only in the edentate sample. The thesis also showed weak evidence of oral impacts predicting memory decline, although the association was marginally non-significant in the full model. Edentulism and oral impacts were strong predictors of subsequent cognitive impairment, independent of many covariates. The association between edentulism and cognitive impairment was significantly mediated by social isolation and preceded by inflammation.

Conclusion: The overall findings of this thesis highlights the importance of oral and cognitive health in a national sample of older people. The results highlight the opportunity for future research to examine the potential effect of oral health in preventing or slowing the onset of dementia.

Impact Statement

The impact of this thesis is mainly to raise the awareness among researchers, dental educators, oral health professionals and policymakers about the potential role of oral health in maintaining better cognitive health, and perhaps lowering the risk of cognitive impairment and neurodegenerative diseases.

For researchers, this thesis, in addition to many other studies, showed some evidence of an association between oral health and cognitive impairment. Researchers across different disciplines need to collaborate and examine the potential effect of oral health on cognition in comprehensive and well-constructed interventional studies. Future studies should focus on examining the effect of restoring a functional dentition and lowering gingival and periodontal inflammation on cognitive health. In addition, it should be noted that social factors and the social pathway have not been explored in the literature previously. It is important for future research to thoroughly explore the social pathway to understand the potential role of social factors in this relationship.

For dental schools and those involved in education and training of dental professionals, this thesis highlights the importance of increasing students' awareness of the potential complications of poor oral health, especially tooth loss, on older people. The effect of tooth loss and edentulism on cognitive health is still underdeveloped in dental education. Dental graduates should be trained to perform different tooth replacement techniques to restore both chewing function and facial esthetic for elderly patients. Additionally, dental education should include more emphasis on the close relationship between oral diseases and Non-Communicable Diseases (NCDs) such as dementia and Alzheimer's disease. Oral disease and NCDs share common risk factors such as unhealthy eating habits, poor nutrition, smoking and excessive alcohol consumption.

For dentists, this thesis raises the importance of preserving the functional dentition to maintain the general wellbeing for older people. Restoring the chewing function should not be delayed and reducing inflammation in the mouth should be a clinical priority in providing dental care for older people.

For policymakers, funding and supporting oral health care for the older population should be a top priority. This could be avoided by improving access to dental care and reducing the difficulties that older populations face when they need dental treatment.

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List of abbreviations

NCDs	Non-Communicable Diseases
ADHS	Adult Dental Health Survey
APA	The American Psychiatric Association
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
WHO	World Health Organisation
MCI	Mild Cognitive Impairment
AAMI	Age Associated Memory Impairment
AACD	Age Associated Cognitive Decline
AD	Alzheimer's Disease
OIDP	Oral Impacts on Daily Performance
MMI	Mild Memory Impairment
mTICS	The Modified Telephone Interview for Cognitive Status
MMSE	The Mini-Mental State Examination
MoCA	The Montreal Cognitive Assessment
3MS	The Modified Mini-Mental State Examination
DSST	Digit Symbol Substitution Test
OR	Odds Ratio
CI	Confidence Interval
SE	Standard Error
CRP	C-reactive protein
HSE	Health Survey for England
HRS	Health and Retirement Study
SEM	Structural Equation Models
WBC	White Blood cell Count

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This thesis is dedicated to my parents, my siblings, my wife and my beloved children.

CHAPTER 1

INTRODUCTION

1 INTRODUCTION

Around 8.5% of the world's population is now over 65 years of age, and this number is expected to increase to 12% by 2030 and to 16.7% by 2050 (He et al., 2016; Radloff, 1977). Similar figures were estimated in the UK with around 21% of the population expected to be over 65 years of age by 2030 (AgeUK, 2019).

Populations ageing and life expectancy, mainly in high-income countries, are rapidly increasing because of many reasons. In the last decades, there was a shift in the profile of the dominant cause of death in older age, Non-Communicable Diseases (NCDs). Compared to low- or middle-income countries, NCDs in high-income countries occur later in life, which means that more people live into adulthood and less premature death. Furthermore, a mixture of improved health care and public health initiatives delayed the onset of NCDs (WHO, 2015). For example, the drop in mortality rates because of cardiovascular diseases and diabetes has increased life expectancy by 3.0 years for men and 4.3 years for women (He et al., 2016). Smoking, which was the leading cause of death, has dropped noticeably in the past three decades (Smith et al., 2016). Fall of fertility rates due to many reasons: families tend to plan fewer children than before, the use of contraceptives has increased and gender norms modification (WHO, 2015).

Living longer is not the only goal. More important than longevity is the quality of the remaining years. To address this aspect, the concept of healthy life expectancy has been developed by the World Health Organization (WHO), which takes into account both mortality and morbidity that affect ageing. There has been a growing interest among public health authorities to maintain well-being at advanced ages to improve overall health (He et al., 2016).

Part of maintaining the general welfare is to preserve healthy and intact brain functions, particularly cognitive health. As populations get older, cognitive impairment becomes more of a public health issue, estimated to be the cause of 40% of the overall admissions to institutional care in the UK and an indication of subsequent dementia (Deary et al., 2009). There were more than 850,000 people with dementia in 2015, and the costs of dementia-related conditions to the UK economy are estimated to be over £24 billion a year (Mitchell et al., 2016).

Another important aspect of the population's health, which deteriorates with age, is oral health. Poor oral health, and tooth loss, in particular, can be an early indicator of frailty in older people (Avlund et al., 2011). The prevalence of oral diseases, e.g., periodontal disease, dental caries and tooth loss, increases with age (Thomson, 2014). According to the Adult Dental Health Survey (ADHS) in England, Wales and Northern Ireland, 29% of participants aged 75 to 85, and 45% of those aged 85 were edentulous in 2009. In the same sample, 60% of participants aged 65 to 84 had at least one periodontal pocket greater than 4 mm (Care and Office for National Statistics, 2012). Hence, the WHO is encouraging public health professionals to plan oral health programmes to improve oral health-related quality of life for older adults (Petersen, 2004).

Furthermore, having poor oral health throughout life can be a risk factor for impaired cognition in the elderly. In the past 20 years, growing evidence suggested the potential association between oral health and cognition (Wu et al., 2016; Nangle et al., 2019; Alvarenga et al., 2019; Cerutti-Kopplin et al., 2016). The literature reported several potential pathways explaining this association, but the two main ones were the inflammatory and the nutritional pathways. Another potential pathway that was not covered in the existing literature, the social pathway, will be assessed in this thesis.

Poor oral health and cognitive impairment share a common inflammatory pathway, and oral pathogens can be a source of inflammation affecting cognitive health (Yaffe et al., 2003). Secondly, chewing impairment due to poor oral health may cause nutritional deficiency. As a consequence, extended periods of poor nutrition could affect cognitive performance and lead to cognitive impairment (Tada and Miura, 2017). Third, discomfort in speaking and eating, and the altered facial appearance caused by poor oral health, may cause social isolation, a risk factor for cognitive impairment (Locker et al., 2000; Shankar et al., 2013). More details about the potential pathways will be explained in Chapter 2 (Section 2.2). Therefore, given that poor oral health is a modifiable risk factor (Pussinen and Kononen, 2016), the purpose of this thesis is to explore and understand the overall associations of oral health with: a) cognitive functioning, b) the change in cognitive functioning, and c) cognitive impairment in an English population aged 50 and above.

1.1 Cognitive decline in older population

When people get older, plaques and tangles gradually accumulate in the brain tissues, which can cause eventually cognitive impairment that also negatively affects routine daily activities (Small, 2016). This process happens “gradually” and the decline in cognitive abilities may take years and vary in speed from person to person depending on many factors. Three phases of cognitive decline have been suggested by clinicians and investigators as follows: cognitive impairment due to normal ageing, mild cognitive impairment (MCI), and dementia (Figure 1.1 retrieved from (Small, 2016)).

Usually, around the age of 50, most people develop what called age-associated memory impairment. This could be forgetting names, misplacing keys or any other personal item, in addition to other cognitive complaints that will not interfere with daily activities. Then, the decline in cognitive functions progresses to a medical condition commonly known as Mild Cognitive Impairment (MCI). Those who develop MCI have an impaired cognition but they are still functionally independent. However, they are at higher risk of developing dementia.

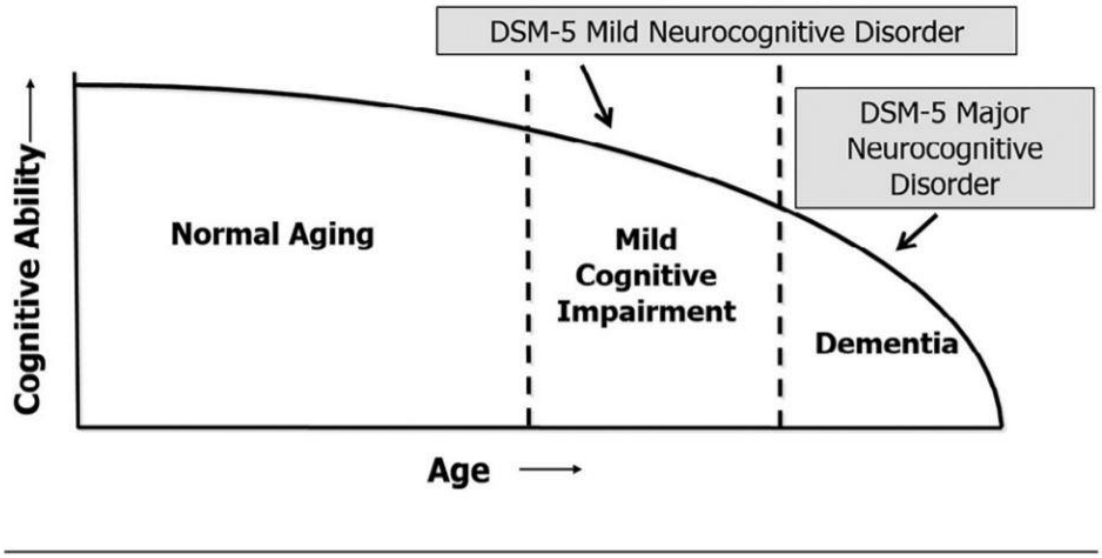

Figure 1.1 A plot of cognitive function versus age shows the expected gradual cognitive decline

The 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) was recently released by the American Psychiatric Association (APA), and the updated manual included new terms: major neurocognitive disorder, which replaces the term ‘dementia’ in DSM-4, and mild neurocognitive disorder, which is

equivalent to the mild cognitive disorder in the WHO International Classification of Diseases (ICD-10) (American Psychiatric Association et al., 2013).

1.1.1 Cognitive functioning

There are six domains of the cognitive function listed in the DSM-5: complex attention, executive function, learning and memory, language, perceptual-motor function and social cognition (Figure 1.2) (Sachdev et al., 2014):

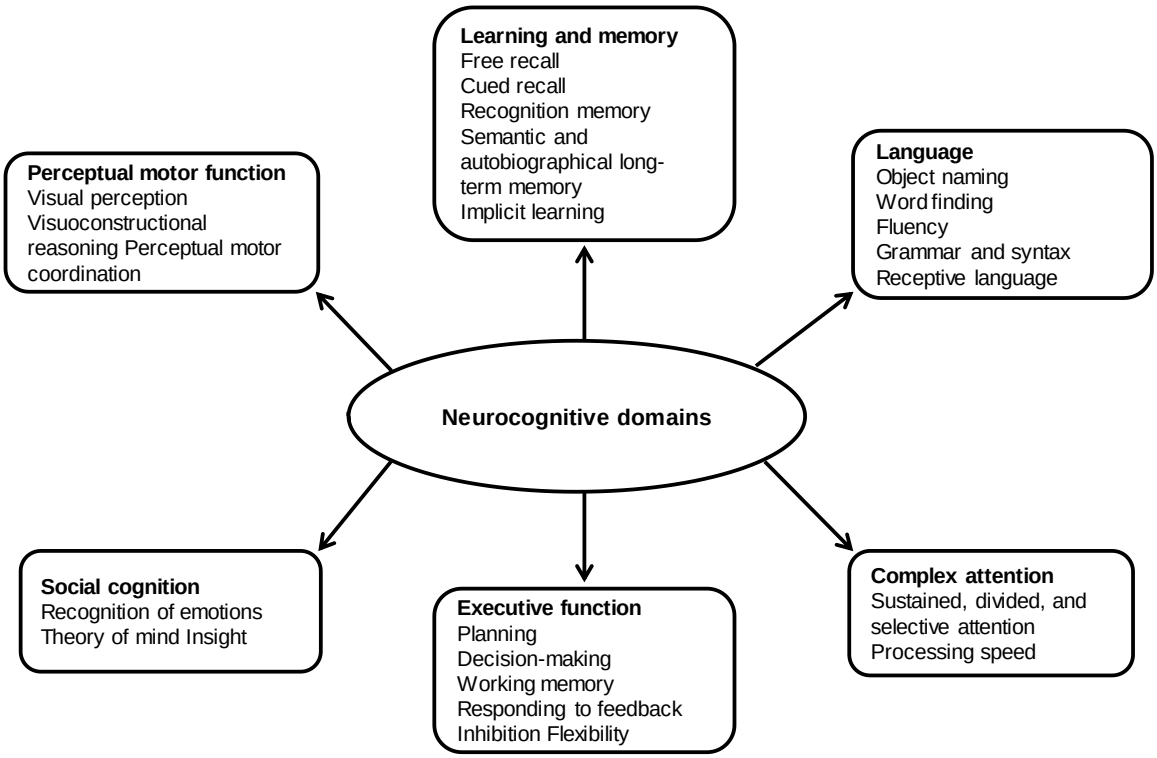

Figure 1.2 The 6 neurocognitive domains in the DSM-5

- **Learning and memory** - includes immediate (free recall, cued recall and recognition memory) and delayed recall memory. The decline in this cognitive domain can be observed when an older person cannot remember a shortlist of items when shopping. Those who are affected by a decline in this cognitive domain require frequent reminders; they get confused about time and place and usually have repetitive behaviour.
- **Executive function** - includes planning, decision making, working memory, responding to feedback, error correction, overriding habits and mental flexibility. If an older person has difficulty in familiar and complex tasks. Those who suffer from a decline in executive functions need external support to plan daily activities and make decisions.

- **Complex attention** - includes sustained attention, divided attention, selective attention and information processing speed. For example, if someone is unable to hold new information such as recalling phone numbers or addresses just given.
- **Language** - includes expressive language (naming, fluency, grammar and syntax) and receptive language. It can be noticed by using general terms such as 'that thing' and 'you know what I mean'. With severe impairment, this may be expressed as an inability to recall names of closer friends/family or familiar people.
- **Perceptual – Motor – Visual perception, praxis** - involves picking up the telephone, handwriting, using a fork or spoon. Significant difficulties with previously familiar activities (using tools or, driving a motor vehicle) and navigating in familiar environments.
- **Social cognition -** includes recognition of emotions and behavioural regulation, social appropriateness in terms of dress, grooming and topics of conversation.

1.1.2 Mild Cognitive Impairment (MCI)

There are several terms for cognitive impairment, such as age-associated memory impairment (AAMI), age-associated cognitive decline (AACD) and mild cognitive impairment (MCI). AAMI is the gradual decline of memory, while AACD is the decline of several cognitive domains in addition to memory due to ageing. The decline for both AAMI and AACD is expected for the age and level of education (Park et al., 2003), while the MCI is the condition which affects cognitive functions beyond of what is expected for the same age and level of education. However, as previously noted, daily functioning is still maintained (Petersen et al., 2001). According to the Alzheimer's Society, MCI cases were estimated between 5% and 20% in a population of 65 years and older in the UK (Alzheimer's Society, 2015). About 10% to 15% of MCI cases progress to dementia in the first year, 20% to 40% in two years, and 30% to 55% in three years of having the symptoms (Perry, 2014).

1.1.3 Dementia

Dementia is a progressive disorder covering several stages of disease progression and usually starts with a pronounced level of cognitive impairment. In the late stages of the disease, people can no longer maintain independent living and

functioning (Arciniegas and Beresford, 2001). By 2040, dementia is expected to affect more than 81 million people worldwide and more than 1.9 million in England and Wales (Ferri et al., 2005; Ahmadi-Abhari et al., 2017). Almost a third of the population of the UK will die from complications of dementia (Livingston and Frankish, 2015; Livingston et al., 2017b). Although there are different types of dementia, there are two that are responsible for almost 90% of all the prevalence: Alzheimer's disease (AD) and vascular dementia. Other types of dementia are less prevalent, Figure 1.3 (Brennan and Strauss, 2014). Since AD is the most common form of dementia, this condition will be explained briefly in the next section. Then, the following section (Section 1.1.3.2) will present the *Commission on Dementia Prevention* published in the Lancet (Livingston et al., 2017b).

1.1.3.1 Alzheimer's disease (AD)

According to the WHO (2017), 60-70% of dementia cases are in the form of Alzheimer's disease (AD). AD begins before any symptoms are perceptible, and usually, starts with subtle symptoms. Eventually, objective cognitive deficit develops, most commonly memory impairment, which can be measured by neuropsychological testing (Perry, 2014). Different neuropathological characteristics of AD vary according to the severity of the disease, such as a progressive loss of synapses and neurones, amyloid deposition, neurofibrillary tangles and noticeable cholinergic deficits. The average survival rate following AD diagnosis is approximately ten years, varying among patients according to the age of onset, the severity of impairment and the presence of other systemic diseases (Hugo and Ganguli, 2014).

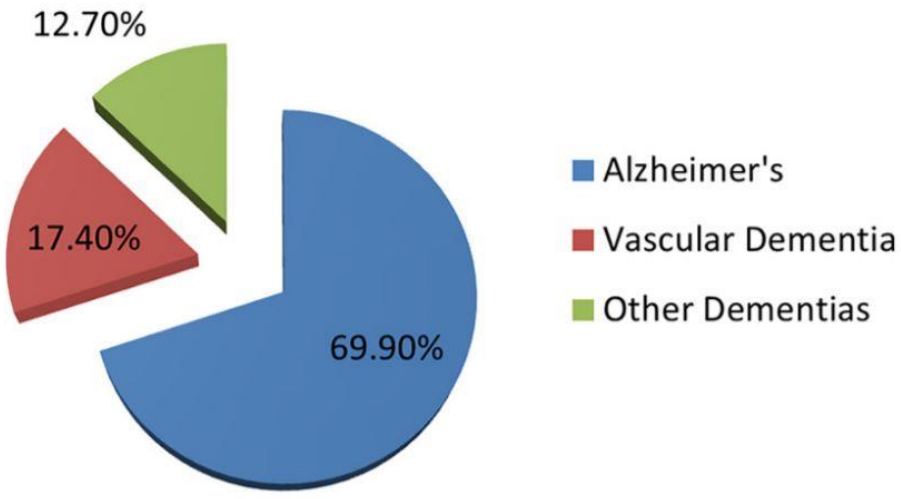

Figure 1.3 Breakdown of dementias

1.1.3.2 Dementia prevention

Recently, the Lancet published a *Commission on Dementia Prevention*, Intervention and Care (Livingston et al., 2017b). The main strategies suggested for dementia prevention were reducing brain inflammation and damage through modifying lifestyle behaviours, such as smoking cessation, physical activity and exercise, controlling depression, obesity, cholesterol and hypertension, and adherence to the Mediterranean diet. Additionally, increasing cognitive brain reserve can prevent dementia through education, cognitive training and intact hearing. Lastly, having a vibrant social network, eating daily fruits and vegetables and moderate alcohol consumption are believed to protect older adults from cognitive impairment, which is a risk factor for dementia.

1.2 Oral health of older population

The burden of oral diseases, globally and in the UK, is enormous. Oral disorders accounted for more than 18 million disability-adjusted life years around the world, according to *the Global Burden of Disease 2017*. This figure has increased by 21% from 2007 to 2017. This means an average health loss of 239 years per 100,000 population due to oral health conditions. The global burden of oral health, tooth loss and periodontal disease in particular, increased considerably from 2010 to 2017 due to population ageing (Kyu et al., 2018b). In England and Wales, older adults have a high probability of edentulism, and among those who were dentate, they are less likely to have functional dentition (≥20 teeth). According to the ADHS, 29% to 40% of older adults had active, untreated dental caries, and 45% had at least one periodontal pocket deeper than 4 mm (Care and Office for National Statistics, 2012).

1.2.1 Dental caries

Caries in the older populations has been confined to either root or secondary caries (caries around existing restorations). However, recent studies showed an increase of primary coronal caries (caries at chewing surfaces) (Thomson, 2014). It could be due to the increased retention of natural teeth among the older population in the last decades (Centers for Disease and Prevention, 2003). In the ADHS, 29%

of those aged 65-74 years, almost 40% among those aged 75-84 and 33% of those aged 85 and older had active caries (Care and Office for National Statistics, 2012).

1.2.2 Periodontal disease

Periodontitis is a progressive destructive oral infection (Cerajewska et al., 2015; Noble et al., 2009) that is considered to be a contributory factor for tooth loss and linked to many chronic illnesses, such as diabetes mellitus and cardiovascular disease (Lockhart et al., 2012; Lalla and Papapanou, 2011). The destruction process affects gingival tissue, periodontal ligament and alveolar bone due to inflammatory changes as a result of the host-response mechanism of more than 400 bacteria colonising periodontal pockets (Paster et al., 2006). In England, among 55 years and older, 65% had a loss of attachment (LOA) 4 mm or more, and 20% had 6 mm or more (Steele et al., 2012). In the ADHS, 60% of those aged 65 to 84 and 47% of those over 85 had at least one deep periodontal pocket (Care and Office for National Statistics, 2012).

1.2.3 Tooth loss

Tooth loss represents an end result of cumulative, lifelong, adverse oral conditions, such as dental caries and periodontal disease (Petersen and Yamamoto, 2005; Gil-Montoya et al., 2015a; Thomson, 2014), and it should not be considered a normal consequence of ageing (Lamster et al., 2016). In *the Global Burden of Disease 2017*, edentulism and severe tooth loss were the primary cause of more than 7 million disability-adjusted life years globally as the most effective oral disorder(Kyu et al., 2018a). The prevalence of edentulism (the status of complete tooth loss) among older adults has declined in the last decades but is still relatively common. In the ADHS, the prevalence of edentulism ranged from 15% of adults aged 65 to 74 and 30% of adults aged 75 to 84 and reached up to 47% of adults aged 85 and older (Care and Office for National Statistics, 2012). In a population-based study of 1,660 older British men aged 71–92 years, 64% of the sample had 20 or fewer natural teeth, and 20% had lost all-natural teeth (Ramsay et al., 2015).

CHAPTER 2

REVIEW OF THE LITERATURE

2 REVIEW OF THE LITERATURE

Many studies in the literature have suggested a bidirectional causality in the association between oral health and cognitive decline and/or impairment (Kaye et al., 2010; Wu et al., 2016; Peres et al., 2015). The first direction is when cognitive decline or impairment affects a person's ability to perform activities of daily living, particularly maintaining good oral hygiene. Poor oral hygiene increases the susceptibility for oral diseases like dental caries, chronic periodontitis and eventual tooth loss. Despite the importance of this direction of the association between oral health and cognition, it will not be covered in this thesis. This thesis will instead be mainly focused on the opposite direction, oral health predicting cognitive health outcomes. The broad goal of this thesis is to add more information about a potential modifiable risk factor, poor oral health, to slow the progress of cognitive decline and delay the onset of irreversible forms of cognitive impairment.

Most of the studies identified in the literature used tooth loss and periodontal disease as the main exposure variable. Oral health measures were collected from self-reported surveys in most studies, and a few from clinical examinations. Different cognitive outcomes were identified: cognitive function, measured either by a single cognitive test (assessing cognitive function domains separately) or by a global cognitive test (assessing the general cognitive health); the change in cognitive functioning which evaluates the severity of cognitive decline over time, and cognitive impairment which utilised a predetermined threshold to stratify participants into impaired cognition versus those who had no impairment.

2.1 Oral health and cognition

In the last few years, several reviews were published presenting the potential associations between oral health and cognition. One was a narrative review (Noble et al., 2013) and the rest were systematic reviews (Nascimento et al., 2019; Nangle et al., 2019; Alvarenga et al., 2019; Tonsekar et al., 2017; Tada and Miura, 2017; Cerutti-Kopplin et al., 2016; Wu et al., 2016).

The earliest review explained the potential links between poor oral health and cognitive impairment (Noble et al., 2013). The review reported that poor oral health could be an unrecognised risk factor contributing to cognitive impairment.

The review also suggested that the association could be mediated by cerebrovascular disease, and stroke in particular. Additionally, the review discussed the potential effect of malnutrition due to tooth loss on cognitive health. Finally, the systematic inflammatory response due to oral diseases was suggested to be another important risk factor of cognitive impairment.

Then, a systematic review of only longitudinal studies by Wu et al. (2016) summarised 16 studies of the association between oral health and cognitive status. The review discussed the bidirectional association between oral health and cognitive dysfunction. From the 16 studies, 11 were focused on the effect of oral health on either the change in cognitive function or the incidence of dementia, and 5 examined the opposite direction. The review reported that the strength of evidence for the association between poor oral health and cognitive function was weak, and findings were often inconsistent.

Another systematic review and meta-analysis focused on the association between tooth loss and diminished cognitive function and concluded that tooth loss increases the risk of cognitive impairment. There were 8 longitudinal studies included in the quantitative synthesis (meta-analysis) and the pooled results showed that individuals with suboptimal dentition (<20 teeth) compared with those with optimal dentition (≥20 teeth) were at higher risk of cognitive impairment. The follow-up periods of the studies ranged between 4 to 32 years, which might explain the differences in the findings (Cerutti-Kopplin et al., 2016).

Furthermore, another systematic review examined the associations between mastication and different cognitive aspects: cognitive function, cognitive decline, cognitive impairment and the incidence of dementia and mild memory impairment (MMI) (Tada and Miura, 2017). The review included 33 articles (22 cross-sectional, and 11 longitudinal studies), and concluded that mastication and cognition might have a close relationship. Most of the prospective cohort studies indicated that poor mastication is one of the risk factors for cognitive decline and a higher incidence of dementia.

Additionally, another systematic review investigated the association of chronic periodontitis and multiple tooth loss with the risk of dementia or cognitive impairment. The review presented evidence from animal experiments (on mice)

and observational (longitudinal) studies. The results confirmed that the relationship between periodontal disease and tooth loss with subsequent cognitive impairment was inconclusive (Tonsekar et al., 2017).

Another recent systematic review and meta-analysis examined the effect of masticatory dysfunction, caused by extensive tooth loss, as a risk factor for cognitive impairment (Alvarenga et al., 2019). The meta-analysis included 9 studies and confirmed that individuals with masticatory dysfunction had a 46% higher chance to have cognitive impairment. However, the level of evidence was rated as low.

Additionally, a recent systematic review by Nangle et al. (2019) reported and summarised the association between oral health and each cognitive function domain. The DSM-5 defines 6 key domains of cognitive function: language, learning and memory, executive function, social cognition, complex attention, and perceptual-motor function. The review reported some evidence of an association of oral health with lower memory function and memory decline; although many of the studies reported non-significant association in the adjusted models. The same association with executive function was inconsistent; although half of the studies reported a significant association.

Finally, the most recent systematic review by Nascimento et al. (2019) inspected the association between periodontitis and cognitive impairment in adults. The search conducted between September and October 2018 and included 8 papers in the qualitative synthesis. The review included only the studies which reported clinical measure of periodontitis and cognitive impairment. The review concluded that Individuals with periodontitis reported a higher probability of developing cognitive decline and suggested an association with cognitive impairment.

2.1.1 Oral health and cognitive function

This section covers studies on the association between different oral health measures and cognitive function (Stewart et al., 2008; Bergdahl et al., 2007; Del Brutto et al., 2014; Matthews et al., 2011; Hansson et al., 2013; Naorungroj et al., 2013a). Tables in Appendix A summarises these studies.

In Sweden, 211 dentate and 188 edentate older participants were selected from a population-based longitudinal study to investigate the cross-sectional

association between the presence of teeth and cognitive function. Cognitive function was measured by 12 different single tests, in addition to the most popular global cognitive test Mini-mental State Examination (MMSE), while oral health was assessed by a self-reported survey. The results showed that having more natural teeth was associated with better cognitive performance in adults aged 50 years and older, although the associations were weak and only for some cognitive tests. The study reported that age and education accounted for most of the variance (Bergdahl et al., 2007).

Another smaller cross-sectional study in Scotland was conducted on 201 participants who were 70 years and older (Starr et al., 2008). The study reported that being edentate was associated significantly with lower cognitive function, measured by the MMSE, and memory score measured by the logical memory test. The association became non-significant after adjusting for age and intelligence. The precision of the estimates of this study might be compromised due to the small sample size.

In the U.S., a cross-sectional study selected two different samples—5,138 adults aged 20-59 and 1,555 adults aged 70 and older—from a large nationally representative data (NHANES III) (Stewart et al., 2008). Various cognitive measures were administered to each age cohort. Participants who were 70 years and older were administered a story recall task to assess memory. Data from a comprehensive oral examination were available. The analyses confirmed that tooth loss was the stronger factor for the story recall test in the older sample; although education attenuated the association substantially.

Moreover, Matthews et al. (2011) analysed the data of 9,853 Caucasian and African American adults 45 years and older. Cognitive function was measured using the word list learning, and tooth loss was self-reported by participants. The results indicated that losing more than 16 teeth, was significantly associated with the mean learning score (ß=−0.16; 95% CI: −0.29 to −0.04); however, after adjusting for wealth and education, the association was no longer significant. It should be noted that the interview with participants made via telephone which could have an effect on the results. It also included younger participants which could make the conclusion on older groups difficult.

Furthermore, a small Danish study was performed in 157 subjects who were 70 years old. The study compared the effect of periodontal inflammation on cognitive function between those who had 10+ missing teeth versus those who had less than 10 missing teeth (Kamer et al., 2012). Cognitive function domains assessed included visuospatial abilities and attention. The study found that participants who had 0–10 missing teeth and periodontal inflammation had lower mean cognitive scores, compared to participants without periodontal inflammation. However, the sample size was slightly small and could compromise the conclusions from the study.

Another study in Sweden included 273 individuals aged 55-80 years, selected randomly from a cohort study of memory, health, and cognition (Hansson et al., 2013). The study analysed the associations between eight different cognitive measures covering several domains and clinically recorded number of teeth. The study reported a positive association between the number of teeth and performance on episodic memory: recall (ß = 0.20; $P < 0.002$) and recognition (ß = 0.24; $P < 0.002$).

Furthermore, a study examined the association between oral health measures and different cognitive tests of 9,874 Caucasians and African Americans with an average age of 62.8 years. The study found that complete tooth loss was significantly associated with lower cognitive scores. The associations for all measures of cognition remained significant after controlling for cigarette smoking, alcohol use and diabetes with a substantial attenuation after adjusting for wealth and education. An increased number of teeth was significantly associated with higher scores of Digit Symbol Substitution and Word Fluency tasks in the fully adjusted models. For periodontal disease, individuals with gingivitis or severe periodontitis had significantly lower cognitive scores (Naorungroj et al., 2013a).

Moreover, Del Brutto et al. (2014) included 274 individuals aged 60 and older who lived in the villages of Ecuador. The sample was selected from a large population-based study to examine the association between edentulism and cognitive function. Cognitive function was assessed using the global Montreal Cognitive Assessment (MoCA), and the number of remaining teeth was dichotomised into two groups— <10 teeth vs. ≥10 teeth based on oral examination. The results showed significant lower MoCA scores for persons with

<10 remaining teeth after adjusting for age, sex and education level, cardiovascular health, depression and dementia (β= -1.06, p=0.03).

Finally, a recent cross-sectional study by Ki et al. (2019) examined panoramic radiographs of 1115 participants aged between 70-84 years to identify the type of tooth replacement and compared it to the cognitive function measured by the MMSE. All participants included in the study had fewer than 20 natural teeth. The study adjusted for many demographic, socioeconomic and health covariates. Tooth replacement groups were: none (reference), pontics only, pontics and implant, and implant only. The study reported a positive and significant association between implant tooth replacement and cognitive function. The association with other groups (pontics only and pontics and implants) were non-significant compared to those who had no tooth replacement.

2.1.2 Oral health and the change of cognitive function

The change in cognitive function was assessed either by a single test evaluating a particular cognitive domain or by a global cognitive test assessing the general cognitive health. For example, word recall test used by different studies to assess the rate of change in memory (Tsakos et al., 2015; Stein et al., 2010a). Other studies used global cognitive tests like the MMSE (Iwasaki et al., 2016; Reyes-Ortiz et al., 2013), which gives a broader overview of cognitive decline. Despite the advantages of the MMSE, this measure also has many limitations: poor sensitivity, test-retest reliability and ceiling effect (Spencer et al., 2013). Other studies combined the scores of different tests to generate a global cognitive test (Stewart et al., 2013). Tables in Appendix B summarises the studies that examined the association between oral health and change in cognitive functioning.

There were some studies which did not include general population samples. For example, Stein et al. (2010b) recruited 144 U.S. Catholic sisters (75-98 years) and followed them for 12 years. The findings showed that individuals carrying Apolipoprotein E (APOE) ε4 or having fewer than 10 teeth, or both, had poorer memory at baseline, measured by the delayed word recall test, and faster memory decline than those with one or neither of these risk factors. These findings were only on a female sample and cannot be generalised to a whole population. Another study included 11,140 type 2 diabetes patients aged 55 to 88

(Batty et al., 2013). It was shown that having fewer teeth increased the risk of cognitive decline but not for days of bleeding gums (an index for periodontal inflammation). The sample selection bias of such studies could compromise the generalisability of the findings.

Furthermore, Reyes-Ortiz et al. (2013) collected data from Mexican Americans older than 65 years across three waves (from 1993-1999). The number of teeth was dichotomised into two groups (0-12 or 13-32), and the change in cognitive function was assessed using the MMSE. Then, the MMSE test measures were divided into memory and no-memory sections. The results showed that those who had 0-12 teeth had a significant drop in the total MMSE score by 0.12 points each year compared to the group with 13-32 teeth. A similar pattern was observed for the no-memory domain with a drop by 0.12 points each year for those with 0-12 teeth compared to those with 13-32 teeth; however, there was no association for the memory section of the MMSE. So, the difference identified (0.12 points) was observed in the total MMSE score and the no-memory section. This study was restricted on specific ethnicity -Mexican Americans, so the generalisability of the study findings on older population from other ethnicities will be difficult.

In a U.S. cohort study, a sample of 947 individuals aged 70 to 79 years was followed for five years (Stewart et al., 2013). Different oral health measures were obtained for tooth loss and periodontal disease, along with different cognitive measures: The Modified Mini-Mental State Examination, Digit Symbol Substitution Test and the clock-drawing test. No significant association was found for any dental measure, except for gingival inflammation which was significantly associated with both cognitive decline and impairment in the fully adjusted models.

In 2015, a study from secondary data analysis in the U.S. reported the association between eight-year change in cognition (1996-1998-2004-2006) and different oral health measures (Naorungroj et al., 2015). The study included 911 adults in the late middle-age with an average age of 64.7 years. All cognitive measures declined over time; however, complete tooth loss, periodontal disease and few teeth at baseline did not predict a greater cognitive decline. The study showed a slower decline in memory function among the edentulous group compared to

dentate. The authors justified this finding by the possible reduction in oral inflammation due to edentulousness, which could happen decades before cognitive function was evaluated during the study.

In a large national English cohort study, Tsakos et al. (2015) examined the effect of total tooth loss on a decline in physical and cognitive functioning over 10 years on 3,166 adults aged 60 and older. The cognitive measure used was the word recall test in six repeated events. Self-reported data were used to report baseline dental status. The results showed a significant association between edentulism and poor memory (ß= - 0.88; 95% CI: -0.66, -1.10), but the association was attenuated after adjusting for socioeconomic variables. Age variation in this association was observed, with significant results in participants aged 60 to 74, but not in those aged 75 and older. The results showed that being edentulous was significantly associated with a higher probability of cognitive decline (OR= 1.77; 95% CI: 1.52, 2.06), however, adjusting for health behaviours lead to a non-significant association. The study had several advantages such as the large representative sample and the long period of follow-up, although cognitive and oral health measures used were limited.

Another small Japanese prospective study of 85 community-dwelling individuals (average age 79.3) reported a significant association between severe periodontitis and the relevant risk of cognitive decline (defined as a drop of more than three scores of the MMSE). The sample size was relatively small, and the follow-up period was quite short (three years) (Iwasaki et al., 2016).

Furthermore, a national Chinese 13-year longitudinal study on 8,153 who were 60 years and older used self-reported number of teeth as the exposure and the change of MMSE as the outcome (Li et al., 2017). The study reported the findings of different sets from linear mixed models and concluded that having more teeth was significantly associated with a slower pace of cognitive decline, adjusting for a large set of potential covariates. The study did not compare dentate versus edentate participants; otherwise, it reported the findings of the interaction of tooth number with time only. The inference about the effect of edentulism (total tooth loss) on cognitive decline cannot be obtained.

Another study was conducted on 2,713 Chinese Americans with an average of 72 years old. The study used tooth symptoms as an exposure variable, although these symptoms were not explained very clearly (Petrovsky et al., 2019). Three different tests were used for each cognitive domain and the global cognitive function test constructed by a composite score of the three measures was also used as a separate outcome. The findings from the linear mixed effect models showed that having teeth symptoms at baseline was associated with faster cognitive decline in the global cognitive test; however, the effect disappears once the model adjusted for sociodemographic factors.

The most recent study was by Iwasaki et al. (2019) compared 179 older participants with severe periodontitis versus those without, and followed them for 5 years. The outcome of interest was the change in MMSE over time, and the results showed that participants with severe periodontitis had a faster cognitive decline in the fully adjusted model. The sample was relatively small, and the confidence intervals were quite large, so the findings should be interpreted carefully.

2.1.3 Oral health and cognitive impairment

A total of 16 studies have been conducted to assess the association between oral health and cognitive impairment, 4 studies were prospective cohort studies (Kaye et al., 2010; Iwasaki et al., 2019; Shimazaki et al., 2001; Okamoto et al., 2015), 2 case-control studies (Gil-Montoya et al., 2015b; Okamoto et al., 2017) and 10 studies were cross-sectional (Stewart and Hirani, 2007; Okamoto et al., 2010; Lexomboon et al., 2012; Park et al., 2013; Saito et al., 2013; Wang et al., 2014; Iwasaki et al., 2015; Peres et al., 2015; Kim et al., 2017; Sochocka et al., 2017). Two of the prospective cohort studies did not include samples from the general population; one was on men only (Kaye et al., 2010) and the other one was on subjects from nursing homes (Shimazaki et al., 2001). The other two showed significant associations of severe periodontal disease (Iwasaki et al., 2019) and edentulism (Okamoto et al., 2015) with cognitive impairment. A summary of studies that examined the association between oral health measures and cognitive impairment is shown in Appendix C.

A six-year prospective cohort study in Japan included 1,929 residents aged 79.7 on average from 29 different elderly institutions (Shimazaki et al., 2001). The

dentition status of the sample, number of teeth and denture use, were recorded by two trained dentists, and mental impairment obtained from the medical records. The study reported a significantly higher incidence of mental impairment in the crude analyses for individuals with fewer teeth and those who were edentate, although the difference was not significant in the multivariable analysis. The findings were from institutionalised individuals and cannot be generalised on the community-dwelling older adults.

In the UK, a national cross-sectional survey was conducted on 2,463 adults over 65 living in households and 1,569 living in care homes (Stewart and Hirani, 2007). Edentulism was assessed using self-reported data. An abbreviated mental test was used to assess cognitive function, and cognitive impairment was defined as having three or more incorrect responses. The results showed a significant association between edentulism and cognitive impairment in the community sample with no association found in the care home sample. The study used a non-validated definition of cognitive impairment, which could make the interpretation of cognitive impairment difficult.

Another study of 597 healthy dentate men, aged 28 to 70 at study baseline, were selected from a prospective cohort study of oral health that began in 1968 (Kaye et al., 2010). The study investigated the potential effect of 32-year oral health data on the risk of having a low cognitive function on either the Mini-Mental State Examination (MMSE) or the spatial copying task. Oral and cognitive health were part of a comprehensive and detailed assessment every 3 years. Low cognitive function was defined as having < 25 points or < 90% of the age- and education-specific median of the MMSE and < 10 points on the spatial copying task. The study showed that, for each tooth lost per decade, the risk of low cognitive function increased 9% to 12%, and, for each tooth that had a progression of alveolar bone loss or periodontal probing, the risk increased 2% to 5%. This study reported findings from 32 years of follow up; although there was a selection bias by having men exclusively in the sample.

In a cross-sectional study by Okamoto et al. (2010), the baseline data from the Fujiwara-Kyo study was obtained. The analysis included 4,206 individuals 65 and older. Oral health was clinically measured including the number of teeth, periodontal status and the age of losing all teeth for edentate participants. The

study used the MMSE to define cognitive impairment and the recall test for memory impairment. The results showed that having 0-10 teeth compared to 22-32 teeth was significantly associated with memory impairment (OR=1.67; 95% CI: 1.07, 2.62) and with low MMSE scores (OR=2.17; 95% CI: 1.51, 3.14).

Furthermore, in another cross-sectional study, 557 Swedish adults aged 77 and older were recruited to examine the association between self-reported chewing ability and tooth loss and cognitive impairment (Lexomboon et al., 2012). A score of ≤12 out of 18 in the shortened version of MMSE was used to assess cognitive impairment, which corresponded to a total MMSE score of ≤23. The crude analysis showed a significant association between cognitive impairment and multiple tooth loss (OR=2.10; 95% CI: 1.35, 3.25) but not in the multivariable analysis.

In Japan, another cross-sectional study included 462 community-dwelling individuals aged 60 and older (Saito et al., 2013). Lower than 23 in the MMSE score was used to define poor cognition. Oral health was assessed by two trained dentists who recorded the number and status of the remaining teeth. After adjusting for potential confounders, 0-10 remaining teeth was an independent risk factor for poor cognition (OR=20.21; 95% CI: 2.20, 185.47). The confidence interval was very large, which could be an indicator of a small sample size of that group (0-10 teeth), and the statistical error could not be ruled out.

Another cross-sectional study included 438 community-dwellers aged 50 years and older lived in Ansan, Korea (Park et al., 2013). All individuals were free from dementia or stroke and had a generally healthy appearance. MMSE was used to define cognitive impairment with a cut-off point of ≤24. The number and location of tooth loss were recorded by an oral examination. The main finding was the significant association between tooth loss and cognitive impairment. The OR (95% CI) for those who lost six to ten teeth was 1.99 (1.08, 3.69) and for those who lost more than ten teeth was 2.26 (1.27, 4.02).

In Sweden, 1,147 individuals aged 60 and older were recruited from a population-based multi-centre cohort study (Nilsson et al., 2014). Two measures of cognition were used—MMSE and clock-drawing test. The cut-off point used to define cognitive impairment was 25, and low cognitive function was defined by having

scores below eight in the clock-drawing test. All participants underwent an oral and radiographic examination to record the number of teeth. The OR (95% CI) of cognitive impairment for the edentulous group was significant 3.2 (1.9, 5.3) in the fully adjusted model. However, for those with few teeth, the association was non-significant. The findings should be treated with caution as the model used was only adjusted for age and level of education, so the effect of other covariates could not be ruled out.

Moreover, a cross-sectional study included a sample from a secondary database looked at the factors associated with tooth loss in older Taiwanese adults (Wang et al., 2014). Cognitive impairment was defined using the MMSE, and the cut-off point for normal cognition was 25 and over. Any scores below 25 were defined as either moderate dementia (MMSE=11-24) or impairment (MMSE<10). In the crude analysis, the OR (95% CI) of having MMSE less than 25 was 1.54 (1.13, 3.9) for those who had fewer than 20 teeth (p-value=0.006). However, the association was attenuated in the multivariable analysis (OR=0.80; 95% CI: 0.43, 2.52) (p-value=0.42).

Furthermore, 409 dentate adults aged 50 years and older were included in a case-control study, 180 with cognitive impairment and 229 without cognitive impairment, to assess whether the periodontal disease was associated with cognitive impairment (Gil-Montoya et al., 2015b). Cognitive impairment for the cases was performed by a neurologist and oral health was assessed by dental examination. Clinical attachment loss was measured to assess periodontal disease and tooth loss used as a proxy for periodontal disease. The findings showed a significant association between AL and cognitive impairment but not for tooth loss. The OR (95% CI) for moderate attachment loss was 2.64 (1.18, 5.92) and for severe attachment loss 2.31 (1.15, 4.66).

Okamoto et al. (2015) conducted a study in a sample of 2,300 adults, 65 years and older, cognitively intact who walk unassisted, selected from the Fujiwara-Kyo study and followed them for five years. The study reported a significant association between total tooth loss and the development of mild memory impairment. A significant association was found between progressing to complete tooth loss and the development of mild memory impairment. The study used the MMSE as a measure of impairment which has several limitations. Also, a high

number of participants did not return for the follow-up visit and were then excluded from the analysis. This could underestimate or overestimate the association, as the proportion of edentate participants and those with low cognitive scores was higher among excluded individuals.

Another population-based cross-sectional study in Brazil (Peres et al., 2015) used self-reported tooth loss as the exposure and severe cognitive impairment, defined by a score lower than 18 in the MMSE, as the outcome. The study reported a significant association between edentulism and severe cognitive impairment. The same association was not significant in the group who had less than 10 teeth in at least one arch. Also, the study declared a higher prevalence of severe cognitive impairment among edentate who are older than 80 years compared to edentate participants in other age groups.

In Korea, a cross-sectional study assessed the cognitive impairment of more than 295 adults 70 and older by the Korean version of the MMSE (cut-off point 20) and chewing efficiency (Kim et al., 2017). The results showed that middle or little chewing ability had a significantly higher risk of cognitive impairment than those with higher chewing ability (OR=7.36; 95% CI: 2.91, 18.60). The wide confidence intervals could be an indication of a compromised statistical power which might interfere with the precision of the results.

More in the association between oral health and cognitive impairment, a case-control study by Okamoto et al. (2017) reported that having fewer teeth was significantly associated with mild memory impairment among those who carry Apolipoprotein E Ɛ4 Allele (APOE). APOE is a known genetic risk factor for cognitive impairment. The sample was obtained from the Fujiwara-Kyo study which was explained earlier in this section.

Another cross-sectional study collected data about periodontal disease clinically and about cognitive impairment measured by the MMSE. The study examined biological markers in a relatively small sample, 128 subjects who were 55-90 years old, and the results reported that having periodontal inflammation and cognitive impairment together resulted in higher systemic inflammation than having one of the conditions alone (Sochocka et al., 2017).

Finally, a recent 5-year longitudinal study by Iwasaki et al. (2019) of 79 subjects with an average age of 80 years. Two qualified dentists performed the clinical examination examined the periodontium of the participants. The study reported that participants who had severe periodontal inflammation are significantly more likely to develop cognitive impairment compared to those without periodontal disease.

Summary of the literature review

The overall evidence was inconclusive and inconsistent for all outcomes of cognition. For cognitive function, although some studies reported significant results, many others reported no association. For the change in cognitive function, only three studies reported significant results between having few teeth and faster cognitive decline, one study was strictly on a female sample, and another was on diabetes patients. Another study reported significant results for the non-memory measures of the MMSE and no association for the memory measures. In contrast, one study reported that edentate participants had slower cognitive decline than dentate participants. For cognitive impairment, there is some weak evidence of an association between tooth loss and cognitive impairment. However, some reported an association between gingival inflammation but not for tooth loss.

2.2 Proposed pathways

Three pathways were considered as the potential responsible mechanisms of how poor oral health could be associated with cognitive decline and impairment: inflammatory, nutritional and social. Two of these pathways, inflammatory and nutritional, were cited by different reviews (Wu et al., 2016; Noble et al., 2013) (Figure 2.1). On the other hand, the social pathway was not presented as such in the literature, though social isolation was suggested as a high-risk factor for cognitive impairment (Locker et al., 2000; Shankar et al., 2013). Therefore, an additional pathway, which is the social pathway, will be examined in this thesis.

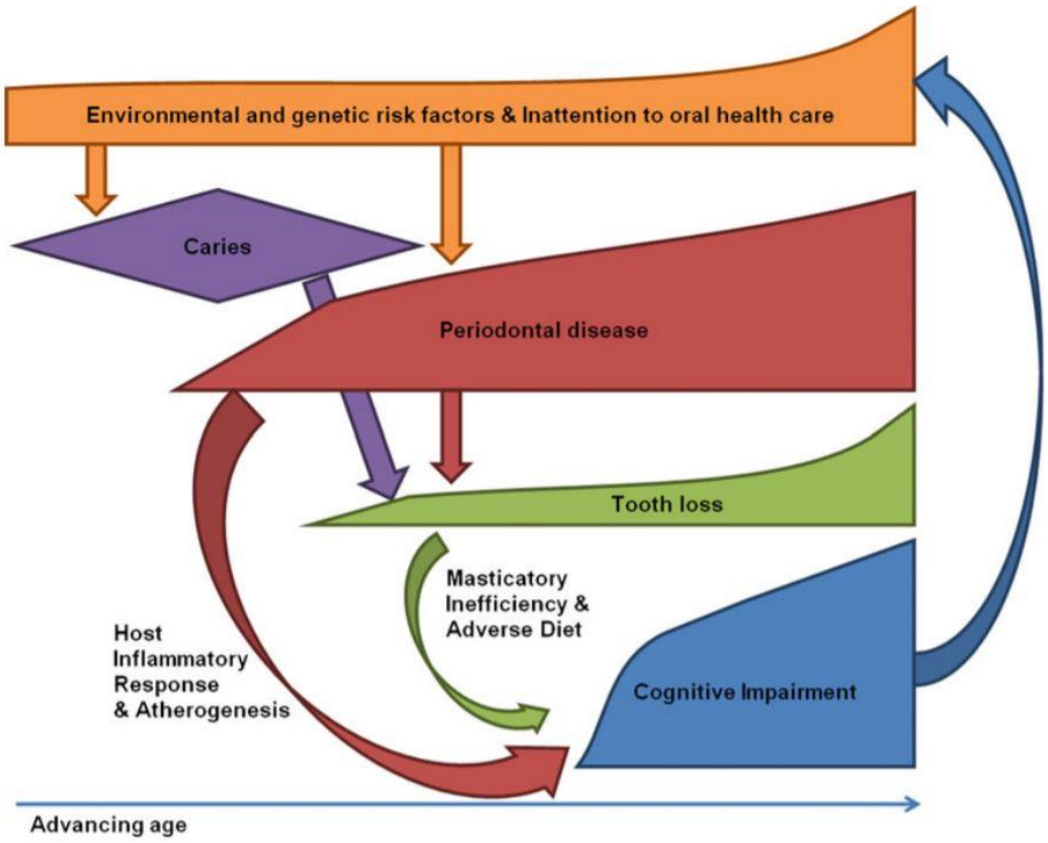

Figure 2.1 Proposed pathway associating poor oral health with cognitive impairment (Noble et al., 2013).

2.2.1 Inflammatory pathway

The inflammatory pathway between oral health and cognitive impairment is linked to the underlying systemic inflammatory response of several periodontal pathogens. Several studies reported the association between high levels of inflammatory markers like interleukin (IL)-6 and C-reactive protein (CRP), which could be released due to the inflammatory response of periodontal disease (D'Aiuto et al., 2004; Matthews et al., 2011), and impaired cognition (Laurin et al.,

2009; Jordanova et al., 2007; Yaffe et al., 2003). Tooth loss may also reflect a tendency towards low-grade inflammation, as measured by increased levels of inflammatory markers, such as the CRP (Lowe et al., 2003). Additionally, in a cross-sectional analysis of large nationally representative data (NHANES III), showed an association between elevated inflammatory markers of the periodontal pathogen (*Porphyromonas gingivitis)* and low cognitive performance among 60 years and older (Noble et al., 2009).

2.2.2 Nutritional pathway

Many researchers reported a minimum of 20 functional teeth (occluding pairs) as the minimum requirement for mastication (Sheiham and Steele, 2001; Marcenes et al., 2003; Naka et al., 2014). Another study reported a high food intake among older individuals with 20 or more teeth compared to those with 19 or fewer teeth (Yoshihara et al., 2005). Similarly, an epidemiological study of adults older than 65 in the UK reported an inverse relationship between tooth loss and adequate dietary intake (Gil-Montoya et al., 2015a). According to Naka et al. (2014), both the number and the distribution of teeth are essential for proper mastication. Another representative British sample of 65 years and older showed a significant effect of total tooth loss on eating habits (Sheiham et al., 2001). As a consequence, the low intake of several B vitamins and antioxidants (Vitamin C and E), which can reduce the risk of cognitive decline, is highly expected due to poor oral health (Tucker et al., 2005; Voko et al., 2003). Likewise, the low consumption of whole grains is linked to higher inflammatory markers and faster cognitive decline (Ozawa et al., 2016). In a systematic review reported by Weijenberg et al. (2011) to outline the importance of mastication on brain functions, the review highlighted an interaction between mastication, nutrition, activities of daily living (ADL), and cognition (Figure 2.2).

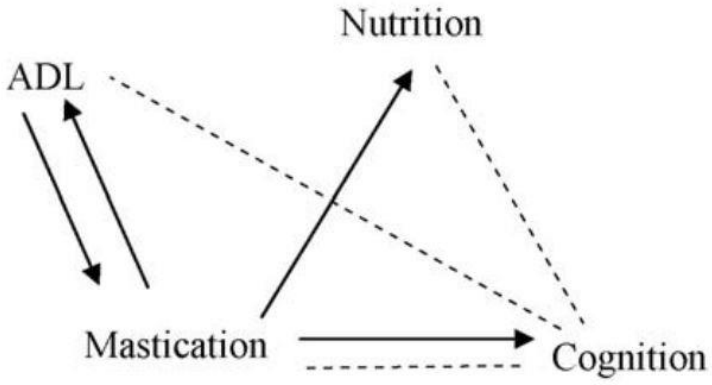

Figure 2.2 The interplay of the various outcomes, arrows indicate causal/longitudinally observed relationships; dotted lines indicate correlations; ADL stands for activities of daily living

2.2.3 Social pathway

Discomfort in chewing and speaking not only limits oral functions but also affects mental health (Locker et al., 2000). Oral health contributes to the quality of life at a biological, social and psychological level. At the biological level, chewing, swallowing, and proper nutrition enhances immunity against systemic infection. At the social and psychological level, the oral cavity is essential for self-esteem, self-expression, facial aesthetics, social interaction and communication (Kushnir et al., 2004).

Poor oral health affects mastication, leading to malnutrition, and changes in pronunciation and poor aesthetics, leading to interpersonal difficulties. As social participation decreases, social disconnectedness and loneliness, stress and depression increases while happiness decreases (Hassel et al., 2011). Another recent study found a significant association between impaired oral health-related quality of life measured by Oral Impact on Daily Performance (OIDP) and loneliness (Rouxel et al., 2017a).

Tooth loss, in particular, affects self-efficacy through functional impairment, fear of stigmatisation and withdrawal from social life (Ehrenthal et al., 2016). According to a longitudinal study of the association between social isolation and loneliness on the change of cognitive function from waves two and four of the English Study of Ageing (ELSA), higher scores of loneliness and isolation were associated with poorer cognitive function at baseline. After four years, loneliness and isolation were associated with poor memory among those low in education, and isolation was associated with poorer cognitive performance at follow-up (Shankar et al., 2013).

2.3 Gaps in the literature

In the past two decades, the research on oral health and cognitive impairment have increased, but the overall findings were inconsistent. This inconclusiveness was observed in all cognitive outcomes: cognitive functioning, the change in cognitive functioning and cognitive impairment.

Some studies showed significant associations between poor oral health and cognitive impairment and/or decline, some showed significant results for only specific groups such as males or females only, and some even showed opposite findings as in Naorungroj et al. (2015) who reported slower cognitive decline among edentulous individuals. Another study (Stewart et al., 2013) found a significant association between cognitive impairment and gingival inflammation only but not for tooth loss and vice versa. Some studies had small sample size such as in (Iwasaki et al., 2016) who included only 85 participants.

This inconsistency could be due to the different measures, for both oral health and cognition, and methodologies used in each study. Also the fact that different studies were conducted on different settings, some on nursing home residents only (Shimazaki et al., 2001), some on both home-dwelling persons and nursing home residents (Stewart and Hirani, 2007), and mostly on community-dwelling people. The literature also was from different countries and populations which have a potentially different lifestyle, cultures, health-care service, etc.

This thesis points out several gaps that need to be addressed through further research:

- Most of the studies identified were only cross-sectional. As such, it would be inappropriate to conclude about the direction of the association and the reverse causation could not be excluded.
- Many longitudinal studies followed subjects for short periods, which might underestimate the association.
- Most of the studies had small and not representative samples.
- Many studies only included specific races or genders. Other studies only included specific populations like nursing home residents or diabetic patients.
- No previous study included self-reported oral health or oral impacts as exposure variables in the association with any of cognitive outcomes.

- Few studies controlled for a broad range of covariates, such as behavioural, psychosocial and biological confounding factors.
- The mediation factors of the potential pathways (inflammatory, nutritional, and social) have never been previously assessed or investigated.
- Only inflammatory and nutritional pathways were suggested in the literature, while the social pathway has never been described in the relevant literature.

This study will address some of these gaps through a detailed longitudinal examination of various oral health and cognitive measures using a large and nationally representative sample of the English population aged 50 and over who were followed for 16-17 years (from wave 0 at 1999 and 2001 to wave 8 at 2016-17). ELSA has a broad range of socioeconomic, behavioural and psychosocial measures and inflammatory markers that can be investigated as potential mediators or confounders.

2.4 Proposed conceptual framework

In this thesis, the focus will be on three main pathways, as presented in the conceptual framework in Figure 2.3: inflammatory, nutritional and social. First, elevated inflammatory markers were found to be associated with cognitive impairment, and oral health could be one of the sources of this inflammatory process (Wu et al., 2016; Noble et al., 2013). Second, oral health, particularly dental caries and periodontal disease, deteriorates with advancing in age, eventually leading to tooth loss (Ramsay et al., 2015; Petersen and Yamamoto, 2005; Gil-Montoya et al., 2015a). As a consequence, edentulism and severe tooth loss are expected to affect mastication and facial aesthetic appearance, which can be a contributory factor for chewing discomfort and lower self-efficacy. This adverse condition may lead to social withdrawal and isolation, thus affecting cognitive health.

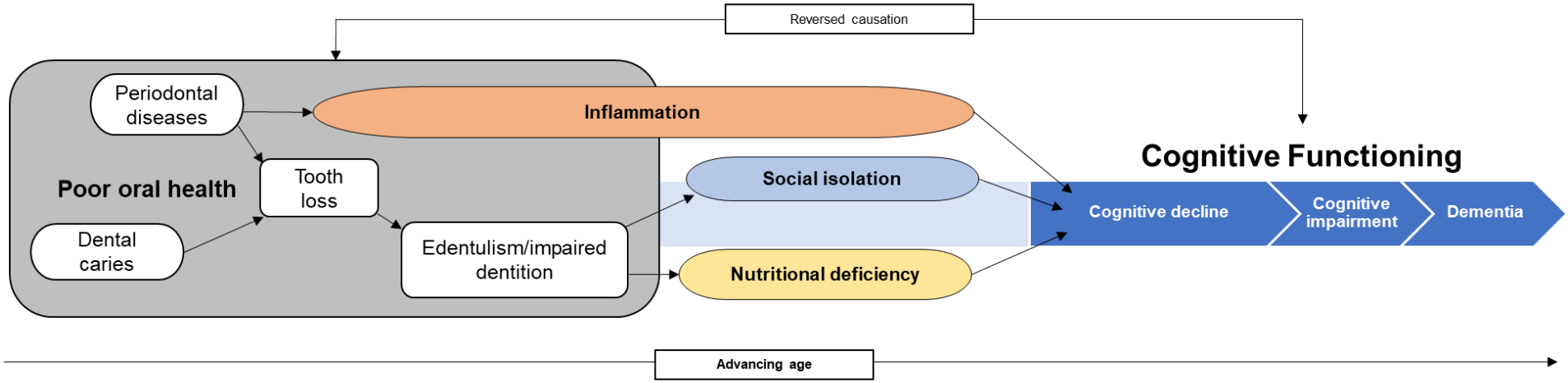

Figure 2.3 Proposed conceptual framework for the association between oral health measures and cognitive impairment and decline in ELSA.

2.5 Aim and Objectives

2.5.1 Aim

The overall aim of the study is to investigate the association between various indicators of oral health with cognitive function, the rate of change in cognitive function and cognitive impairment in a national sample of older adults 50 years and over from ELSA.

2.5.2 Objectives

Objective 1 - To investigate the cross-sectional association of different oral health measures (self-reported oral health, edentulism and oral impacts) with cognitive function (memory and executive function) at wave 3.

Objective 2 - To investigate the longitudinal associations of various oral health measures (self-reported oral health, edentulism and oral impacts) at waves 3 with cognitive function (memory and executive function) at wave 8.

Objective 3 - To investigate the longitudinal associations of various oral health measures (self-reported oral health, edentulism and oral impacts) at waves 3 with the rate of change in cognitive function (memory and executive function) from wave 3 to wave 8.

Objective 4 - To investigate the longitudinal associations of various oral health measures (self-reported oral health, edentulism and oral impacts) at wave 3 with the subsequent cognitive impairment at wave 8.

Objective 5 - To investigate the role of mediating factors (inflammatory, nutritional and social) at wave 6 in the associations between oral health measures (edentulism and oral impacts) at wave 3 and cognitive impairment at wave 8.

Objective 6 - To investigate the role of inflammation, assessed by inflammatory markers (CRP and fibrinogen) at wave 2, as a precursor in the associations between edentulism at wave 3 and cognitive impairment at wave 8.

METHODOLOGY

3 METHODOLOGY

This study is based on the secondary analysis of data from ELSA. This chapter will summarise the methodology of ELSA, a brief description of study design, methods of data collection and an overview of relevant waves.

3.1 Introduction of the ELSA dataset

ELSA is a multidisciplinary biennial longitudinal study that follows a nationally representative community-dwelling sample of men and women aged 50 years and older from England (Zaninotto and Steptoe, 2019). It is mainly funded by the National Institute of Ageing and a consortium of British Government Departments including the Office for National Statistics. Ethical approval was obtained from the Multi-Center Research Ethics Committee.

The original sample has been drawn from individuals who previously participated in the Health Survey for England (HSE), an annual cross-sectional household survey that investigates a broad range of health data and biometric measures. ELSA's first-wave of participants were recruited from three survey years of the HSE—1998, 1999 and 2001—and wave 1 started in 2002-03. ELSA-eligible participants from the three waves combined in wave 0. Eligibility criteria were as follows: membership of a participating household from HSE, was born on or before 1 March 1952 and had been living in a participating HSE household and were, at the time of the ELSA interview (2002-03), still living at a residential address in England. In addition to the target sample, partners who were in the household and were aged <50 years were invited for an interview. All participants who were recruited for ELSA wave 1 or were partners of the core member are known as Cohort 1. In wave 2 (2004-05), the participants and their partners were eligible for an additional interview if they had not refused any further contact after the first interview. Wave 3 occurred in 2006-07, wave 4 in 2008-09, wave 5 in 2010-11, wave 6 in 2012-13, wave 7 in 2014-15, and wave 8 in 2016-17, and wave 9 has been completed but not yet released. As the study progressed and the original sample was getting older, the sample was refreshed with new individuals (from the HSE database) at waves 3, 4, 6, 7 and 8 to represent the younger ages in the chosen age group.

Figure 3.1 shows an overview of the structure of ELSA waves 1-8. Further information and details about ELSA are described elsewhere (Banks et al., 2003)

and all questionnaires are available from the ELSA website and the data available from the UK Data Service website (UK Data Service, 2019; ELSA, 2019).

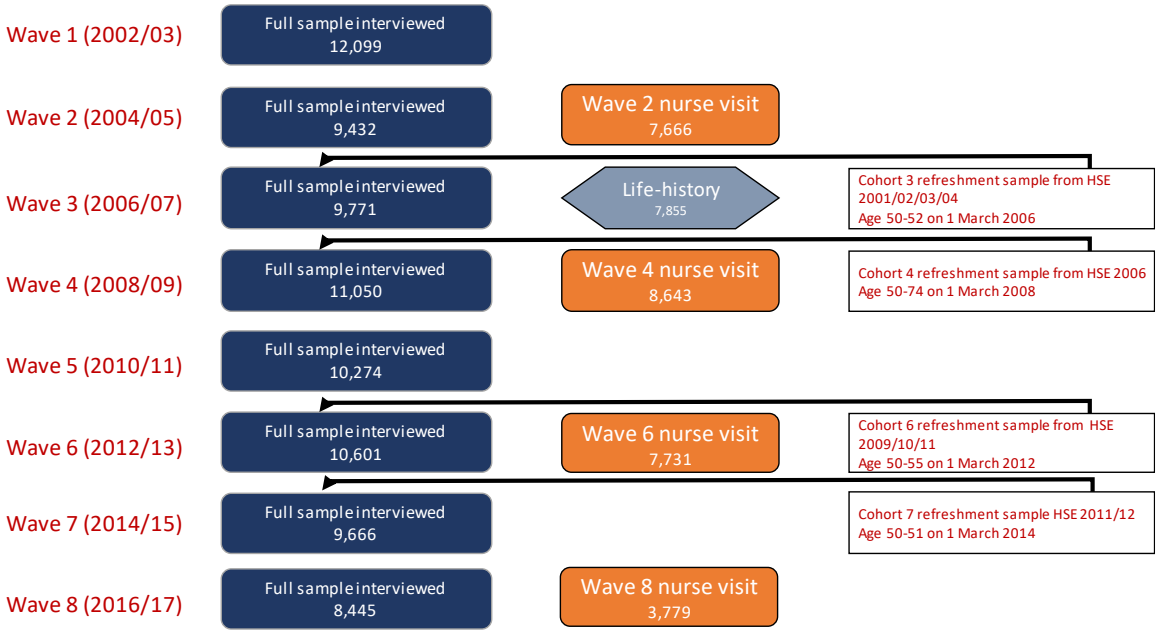

Figure 3.1 An overview of the structure of ELSA from wave 1 to wave 8.

3.2 Data collection in ELSA

At each wave, all participants were interviewed face-to-face and responded to a self-completion questionnaire. Although the aim was to collect the same data throughout the waves, some new questions have been added, and other questions were omitted in some waves. However, most of the questions remained the same through all the waves.

The nurse visit was a face-to-face interview where biological samples, anthropometrical measurements and measures of physical functioning were collected. Participants in all cohorts gave full informed consent for participation, and ethical consent has been obtained for all waves and components of ELSA, according to the ethical approval system in operation at the time.

3.2.1 Computer-Assisted Personal Interviewing (CAPI)

The main CAPI interview takes the form of a face-to-face interview and contains various modules, each covering a different area of enquiry, such as household demographics, individual demographics, health, social participation, work and pensions and psychosocial.

3.2.2 Self-completion questionnaire

The main paper self-completion questionnaire asks about the participants' quality of life, social participation, control at work, life satisfaction, social network, diet and alcohol consumption, among others.

3.3 Data selection: waves of ELSA used in this thesis

This study uses both cross-sectional and longitudinal individual-level data from the ELSA study waves 2 (2004-05) to wave 8 (2016-17). Wave 3 (2006-07) was selected as the baseline for the thesis as the oral health exposure variables (self-reported oral health, Oral Impacts on Daily Performance (OIDP) and edentulousness) were included for the first time at this wave of ELSA. Wave 2 was included in this thesis to obtain the data for inflammatory markers to be used as a precursor in the association between oral health and cognitive impairment in chapter 8. ELSA has different cognitive function measures; however, they were included and removed in different waves. Memory test (immediate and delayed word-list recall) was available at all waves; while the test for executive function was only missing at wave 6 but available at all other waves. A detailed description of all the measurement of variables is presented in the following sections of this chapter.

3.3.1 Analytical sample for the cross-sectional analysis

In this analysis, as a first step, the cross-sectional association between oral health and cognitive functioning using complete data from wave 3 (2006-07) was examined (results in Chapter 4). All ELSA core members were eligible for the analysis, except members who reported doctor-diagnosed dementia, Alzheimer's disease, and Parkinson's disease. Oral health measures used were self-reported oral health, edentulism and oral impacts (evaluated through the OIDP). Cognitive function domains analysed were memory and executive function. The sample for the cross-sectional is denoted in Figure 3.2 as Sample 1.

3.3.2 Analytical samples for the longitudinal analysis

The analytical samples for the longitudinal analyses were different according to the specific objectives and analytical approach which has been used. Figure 3.2 shows the criteria of exclusion for each sample.

The first longitudinal analytical sample, (Sample 2) used in the time-lag and autoregressive linear and logistic regression analyses to approach the results in Chapter 5 and Chapter 7, and in parts of the Structural Equation Models (SEM) pathway analysis in Chapter 8. In this sample, any new cases of doctor-diagnosed dementia, Alzheimer's disease and Parkinson's disease were excluded. Participants who did not participate or had missing data on cognitive functioning at wave 8 were excluded.

The second longitudinal analytical sample, (Sample 3) used to assess the impact of oral health on the rate of cognitive function change- results in Chapter 6. This sample included the maximum number of available observations from waves 3 to 8 because of the ability of the *linear mixed-effects model* in handling missing data. However, the mixed models can only estimate a specific random effects parameter if there are multiple observations for each level of the random effects grouping factor and the fixed effects parameter to which one wants to add the random effects parameter. If there is only one observation for each level of the random effects grouping factor, the random effects parameter is confounded with the residual variance and cannot be uniquely identified. Mixed models require multiple observations for each level of the random effects grouping factor and each factor that varies within the random effect (Singmann and Kellen, 2017). Therefore, anyone from the participants who had only one observation been excluded from the final sample.

Finally, the last longitudinal analytical sample (Sample 4) included in the SEM models to assess the role of inflammation at wave 2 as a precursor in the association between oral health at wave 3 and cognitive impairment at wave 8. In this set of analyses, including inflammatory markers from wave 2 led to additional missing observations which were excluded from the final sample.

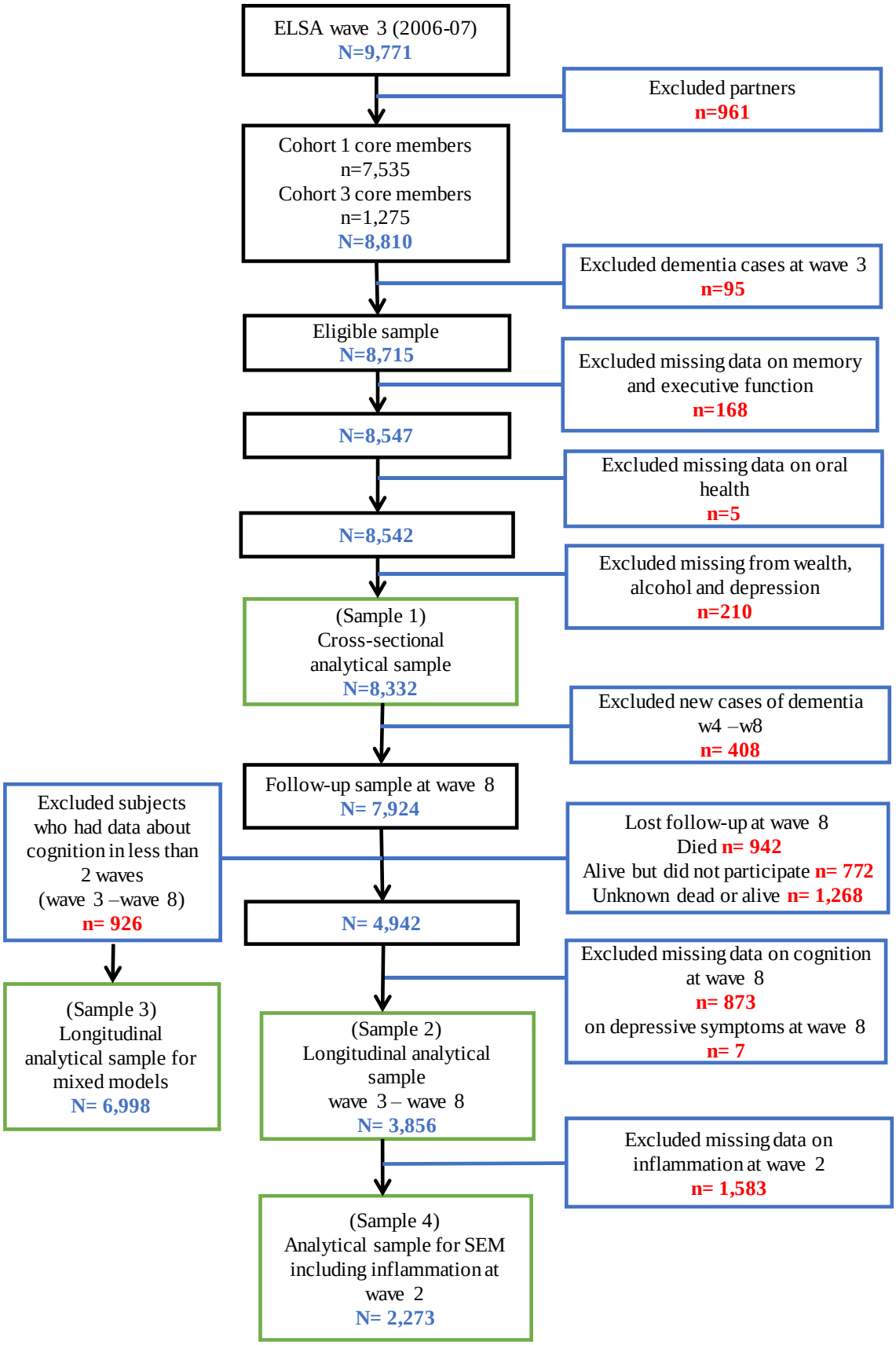

Figure 3.2 The origin of the ELSA study sample and the analytical samples used in this thesis – after exclusion criteria and loss to follow-up, ELSA wave 3 - wave 8

3.4 Outcome variables

In this project, three relevant cognitive outcomes were evaluated. The outcomes included: cognitive functioning, change in cognitive functioning and cognitive impairment.

3.4.1 Cognitive functioning

The first step in this thesis was to analyse the association between oral health and cognitive function, cross-sectionally at wave 3 (Objective 1) and longitudinally at wave 8 (Objective 2). Two cognitive domains were selected to assess cognitive function: memory and executive function. For memory, immediate and delayed word-list recall test was selected (Folstein et al., 1975), while for executive function, word-finding (animal naming) was selected (Roth et al., 1986). Both were treated as continuous variables and results are shown for the cross-sectional analysis in Chapter 4 and for the longitudinal analysis in Chapter 5.

3.4.1.1 Memory

The word-list recall test is part of the widely used Mini-Mental State Examination (MMSE) and other standard test batteries used for cognitive assessment (Folstein et al., 1975). It is one of few cognitive measures that has been repeated in all ELSA waves. The word-list recall test assesses verbal learning and memory, and the score ranges from 0-20, 10 for immediate and 10 for delayed recall. During the test, 10 common words were presented, and the participants were asked to recall them, both immediately and after a short delay, filled with other cognitive tests. ELSA uses the word lists developed for the Health and Retirement Study (HRS) (Steffick, 2000), which comprise four different versions, so that various lists can be given to different members of the same household, and for different waves. The list of words used in ELSA is presented in Appendix D.

3.4.1.2 Executive function

Animal naming is a commonly used test of verbal fluency, and the current version in ELSA was taken from the cognitive assessment section of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Roth et al., 1986). This test assesses how quickly participants can think of words from a specific category, in this case naming as many different animals as possible in one minute. Successful performance on this test requires self-initiated activity, organisation and abstraction

(categorising animals into groups such as domestic, wild, birds, dogs) and set-shifting (moving to a new category when no more animals come to mind from a previous category). The test requires efficient executive function with higher control of language, retrieval ability, attention and demands on frontal structures (Gladsjo et al., 1999). An example of animal naming from the cognitive booklet used in ELSA is presented in Appendix D.

3.4.2 The change in cognitive functioning

The second step in this thesis (Objective 3) was to assess the impact of oral health on cognitive change (i.e., whether oral health status can be linked to the rate of change in cognition- mostly a decline). The same measures mentioned in the cognitive functioning section (the word-list recall and the animal naming) were used to assess the rate of change in mixed-effects models. The rate of change in cognitive function was assessed from wave 3 to wave 8.

3.4.3 Cognitive impairment

The last step in this thesis was to examine the association between oral health and the impairment of cognition (Objective 4). Cognitive impairment or what is commonly known as a Mild Cognitive Impairment (MCI) is an impairment in one of the cognitive domains beyond to what is expected for the same age and level of education, but do not interfere with daily activities (American Psychiatric Association et al., 2013). Also, this variable was used to investigate different pathways related to this association (Objectives 5 and 6), cognitive impairment was ascertained using the modified version of Telephone Interview for Cognitive Status (mTICS) (Brandt et al., 1988). Although there is no “gold standard” operational criterion for diagnosis cognitive impairment, several studies suggested the cut-off point for the scores to fall more than 1.5 Standard Deviation (SD) below age-appropriate norms on a cognitive test battery (Petersen and Morris, 2005; Jak et al., 2009). The following section will demonstrate the test battery used in ELSA-mTICS, in details.

3.4.3.1 The modified version of TICS (mTICS)

The mTICS is a test battery modified from the original TICS (Brandt et al., 1988) which has been applied by the HRS (Plassman et al., 2007). It combines the scores of the following cognitive tests: the immediate and delayed word-list recall test, time

orientation, person orientation, object naming, serial of 7s subtractions and backward counting (Table 3.1). The battery score ranges from 0 (severely impaired) to 35 (high cognitive functioning). The 35-point mTICS included a number of cognitive tests which assess different cognitive domains. The test has high sensitivity and specificity for cognitive impairment in community samples of older adults (Welsh et al., 1993; de Jager et al., 2003). The criterion which used to diagnose cognitive impairment in this project was any score fall more than 1.5 SD below age-appropriate norms mTICS. More details about the 6 elements of mTICS test battery are presented below.

Table 3.1 Cognitive tests included in the mTICS out of 35

Test	**Score**
1- Word-list recall: Immediate and delayed	0-20
2- Time orientation	0-4
3- Person orientation	0-2
4- Object naming	0-2
5- Serial of subtractions	0-5
6- Counting backwards	0-2
Total score	0-35

3.4.3.1.1 Word-list recall: immediate and delayed

The word-list recall test evaluates verbal learning and memory, and the scores range from 0-20, 10 for immediate and 10 for delayed recall. During the test, 10 common words were presented, and the participants were asked to recall them, both immediately and after a short delay, filled with other cognitive tests.

3.4.3.1.2 Time orientation

Orientation is one's understanding of the self and the relationships between the self and our environments both in the past and in the present. Place, time and person are the common categories of orientation. These questions were primarily adapted from the Mini-Mental State Examination (MMSE) test. ELSA had questions on time orientation eliciting the date (day, month, and year) and the day of the week. Each correct answer was scored 1 point.

3.4.3.1.3 Person orientation

The questions on person orientation asked the respondents to name the current heads popular nations (Current UK Prime Minister and current US president). If

the respondent mentioned only the first name, then the answer is not correct. The correct answer should be by giving the last name.

3.4.3.1.4 Serial of subtractions

Respondents were asked to conduct 5 consecutive subtractions of 7, starting from 100. Each correct answer was scored 1 point. Respondents who refused to perform the test at the outset or who began the test and refused midway through were assigned missing values.

3.4.3.1.5 Backward counting

The backwards counting exercise required respondents to count consecutive numbers backwards from 20. Respondents were allowed two trials. For a correct count on the first trial, the participant received 2 points, and a correct response on the second trial was scored with 1 point. Respondents who refused to attempt either trial were assigned a missing value.

3.4.3.1.6 Object naming

The respondent is asked the name of the object used to cut paper. Scissors or shears are marked as correct responses. A second question asks the respondent to name the prickly plant that grows in the desert. Either the word “cactus” or the name of a type of cactus is considered a correct response.

3.5 Exposure variables: oral health measures (Wave 3)

Previous validation studies of oral health measures reported that self-assessment of clear and salient conditions, such as the number of teeth or having a denture, can be reported reliably (Liu et al., 2010; Pitiphat et al., 2002). Therefore, in this thesis, 3 self-reported oral health variables were selected as the main exposure variables: self-reported oral health, edentulism and oral impacts.

3.5.1 Self-reported oral health

The self-reported oral health is a broad multidimensional subjective assessment of oral health. It reflects current oral health status, but it also gives an indication about the mood and emotional state of the respondent (Locker et al., 2005). Three categories were derived from the Likert scale of the variable as follows: excellent, good and poor. It is a significant health indicator strongly associated with functional decline and mortality (Lee, 2000; Winter et al., 2007) and a valid indicator of overall oral health status, particularly at an advancing age (Matthias et al., 1995).

3.5.2 The presence of no natural teeth (edentulism)

ELSA participants were asked: 'in relation to dental health, which of the following applies to you?' choosing from four categories: "no natural teeth and wear denture"; "both natural teeth and denture(s)"; "only natural teeth"; "neither natural teeth nor dentures". A dichotomized variable was derived: dentate (having natural teeth) versus edentate (not having any). Many studies used edentulism as a measure of poor oral health to assess the effect of tooth loss on cognition (Naorungroj et al., 2013b; Tsakos et al., 2015; Del Brutto et al., 2014).

3.5.3 Oral impacts

This variable was assessed by using five commonly reported performances included in Oral Impacts on Daily Performance (OIDP) by using the following question: "In the past six months, have any problems with mouth, teeth or dentures caused any of the following conditions?". There were six possible answers:

- Difficulty eating food;
- Difficulty speaking clearly;
- Problems with smiling, laughing and showing teeth without embarrassment;
- Problems with emotional stability, for example, becoming more easily upset than usual;
- Problems with enjoying the company of other people such as family, friends, and neighbours;
- None of these.

Experiencing oral impact was treated as a binary variable differentiating respondents who reported at least one oral impact and those who reported none. OIDP is an internationally well-known valid and reliable measure of oral health-related quality of life (OHRQoL) (Tsakos et al., 2001).

3.6 Covariates

Additional variables identified as significant potential covariates were demographic factors (age, sex and marital status), socioeconomic factors (education and wealth) lifestyle behaviours (alcohol consumption and smoking) and depressive symptoms.

3.6.1 Age

Age was coded into the following three groups to reflect different stages of life: 50-64 years; 65-74 years; and 75 years and older. These stages include: a group of older adults that are still at working age (50-64), an age group that reflects the first decade of being pensioners (65-74) and finally an age group that refers to the very old adults (75 years and older).

3.6.2 Sex

Sex was coded as: (0) male; and (1) female.

3.6.3 Marital status

Respondents were asked about their current marital status. The response options were: single who never be married; married; legally recognised civil partnership; legally separated; divorced; widowed. For the analysis, three groups were constructed accordingly: currently in a relationship (married or partnered), not in a relationship (single), previously in a relationship (legally separated; divorced; widowed).

3.6.4 Level of education

The education variable used was the highest formal educational qualification achieved as opposed to years of schooling, partly due to differences in the compulsory school leaving age for the cohorts in our sample. The low education group is defined as those with no qualifications or less than O levels (or equivalent). The medium education group is defined as those with O levels, or equivalent and the high education group is defined as those with A levels or higher. Socioeconomic factors are strongly associated with health among older adults (Robert et al., 2009). Educational, in particular, has repeatedly shown a substantial effect on cognition in older people, either directly through the provision of cognitive reserve or indirectly through the occupational route (Lenehan et al., 2014). Highly educated people are expected to attain good jobs, which provide cognitively stimulating tasks. These, in turn, enhanced cognitive functioning in older age.

3.6.5 Total net household wealth

The second socioeconomic factor assessed was the total non-pension household wealth. It included the financial wealth (savings and investments), the value of any

home and other property (less mortgage) and the value of any business assets and physical wealth, such as artwork and jewellery, net of debt. Wealth is the most robust indicator of socio-economic circumstances in ELSA and has been found to be more strongly associated with the risk of death than any other socioeconomic position indicator at older ages (Demakakos et al., 2016).

3.6.6 Alcohol

In ELSA, participants were asked about the frequency of alcohol consumption in the past 12 months. Responses varied from ‘almost every day’ (1) to ‘not at all in the past 12 months’ (8). A dichotomous variable for drinking was derived as follows: daily drinking for those who drink more than five days per week and less than daily for those who drink fewer than five times per week. Studies have suggested that alcohol consumption, within limits and/or of certain types, is associated with a decreased risk of cognitive impairment. It has been suggested that flavonoids in wine have an antioxidant effect on brain tissues (Polidori, 2003; Commenges et al., 2000; Standridge, 2004). Nevertheless, chronic alcohol abuse is believed to cause progressive neurodegenerative disease (Zuccala et al., 2001).

3.6.7 Smoking

Three categories of smoking were used in this project: current smokers, former smokers and those who never smoked. Smoking has been consistently linked to many negative outcomes, including cognitive impairment, among older adults (Sabia et al., 2012; Durazzo et al., 2010; Peters et al., 2008; Chang et al., 2014).

3.6.8 Depressive symptoms

Depressive symptoms in ELSA were measured by the shortened version of the Centre for Epidemiological Studies-Depression (CES-D) scale (Radloff, 1977; Steffick, 2000). A dichotomous variable for depressive symptoms was derived using the validated cut-off point of 4 or more on CES-D 8 items. Depression is a common condition that tends to co-exist with impaired cognition and it’s often considered a prodromal phase to dementia (Pellegrino et al., 2013).

3.7 Variables used in pathway analysis

For chapter 8, additional variables were used to investigate the role of different pathways in the association between oral health and cognitive impairment. Pathways analysed were inflammatory, social and nutritional.

3.7.1 Inflammatory markers

Inflammatory markers in ELSA were high-sensitivity C-Reactive Protein (CRP), White Blood cell Count (WBC), and plasma fibrinogen and all were treated as continuous variables. CRP (mg/L) was analysed using the N Latex CRP mono Immunoassay on the Behring Nephelometer II Analyzer (Dade Behring, Milton Keynes, UK) (Spronston K, 2006). Participants with values of CRP > 10 mg/L were excluded since it is most likely cases of acute inflammation and immune activation due to current infection rather than a chronic inflammation (Lassale et al., 2018).

Fibrinogen analysis was carried out by the Organon Teknika MDA 180 analyser using a modification of the Clauss thrombin clotting method. Both markers, CRP and plasma fibrinogen, were used in several studies as systemic low-grade inflammatory markers (Tampubolon, 2016; Frank et al., 2019). The WBC was not measured in wave 2, and relevant data were available starting from nurse visit at wave 4. The WBCs considered a reliable biomarker of inflammation (Wirth et al., 2018).

Since both the Health Survey for England (HSE) and ELSA applied the same guidelines and the same laboratory protocols for the blood analyses, further details of the blood sample analyses, the internal quality control, and the external quality assessment of the laboratory can be found in the 2004 HSE technical report (Spronston K, 2006). Several studies have suggested that low-grade peripheral systemic inflammation is associated with faster cognitive decline and reduced hippocampal volume (Marsland et al., 2008; Yaffe et al., 2004). The levels of inflammatory markers are measured from blood samples drawn at each nurse visit, and their level increases if inflammation exists in the body.

3.7.2 Social isolation

Social isolation in ELSA was assessed through an index which included the level of contact with the participant's social network and the involvement in social organizations (Schrempft et al., 2019; Rafnsson et al., 2017). Three categories of

social ties were included to form the index: children, family other than spouse and children (e.g., cousins), and friends. Participants responses included: less than once a year or never, once or twice a year, every few months, once or twice a month, once or twice a week, and three or more times a week. According to Cohen et al. (1997), 1 point was given if the respondent had less than monthly contact (including face-to-face, telephone or written/e-mail contact) with each category or social tie. Participants were given an additional point if they did not participate in any organizations such as social clubs, sports clubs, churches or residents' groups. Scores ranged from 0 to 4, with higher scores indicating greater social isolation. Social networks believed to have a positive influence on cognition and a protective effect against dementia onset among older adults (Stoykova et al., 2011; Crooks et al., 2008; Rafnsson et al., 2017).

3.7.3 Nutrition

In ELSA, nutrition was assessed by the number of fruit and vegetable portions consumed every day. Participants were asked about the number of vegetable portions, excluding potatoes, eaten on a typical day. A serving or portion of vegetables means three heaped tablespoons of green or root vegetables such as carrots, parsnips, spinach, small vegetables like peas, baked beans or sweet corn, or a medium bowl of salad (lettuce, tomatoes, etc). Participants answered a similar question for fruit consumption. A portion of fruit is an apple or banana, a small bowl of grapes, or three tablespoons of tinned or stewed fruit. Only one glass of fruit juice counted per day, any additional glasses of fruit juice do not count as additional portions. Nutrition was treated as a continuous variable. There is evidence suggested that higher fruit and vegetable consumption was linked to a lower risk of cognitive impairment in the older population (Roberts et al., 2010).

3.8 Overview of the analytical approaches

To achieve the aim and objectives of this thesis, different analytical approaches were implemented. Figure 3.3 summarises the analytical framework used in this thesis. Results in all the analyses were considered as statistically significant if the p-value is below the 0.05 limit. Descriptive analyses and logistic regression models were carried out using STATA software version 15SE (StataCorp, 2007) and the Mplus version 8.1 was used for path analysis and the Structural Equation Models (SEM) presented in Chapter 8 (Muthén and Muthén, 2019).

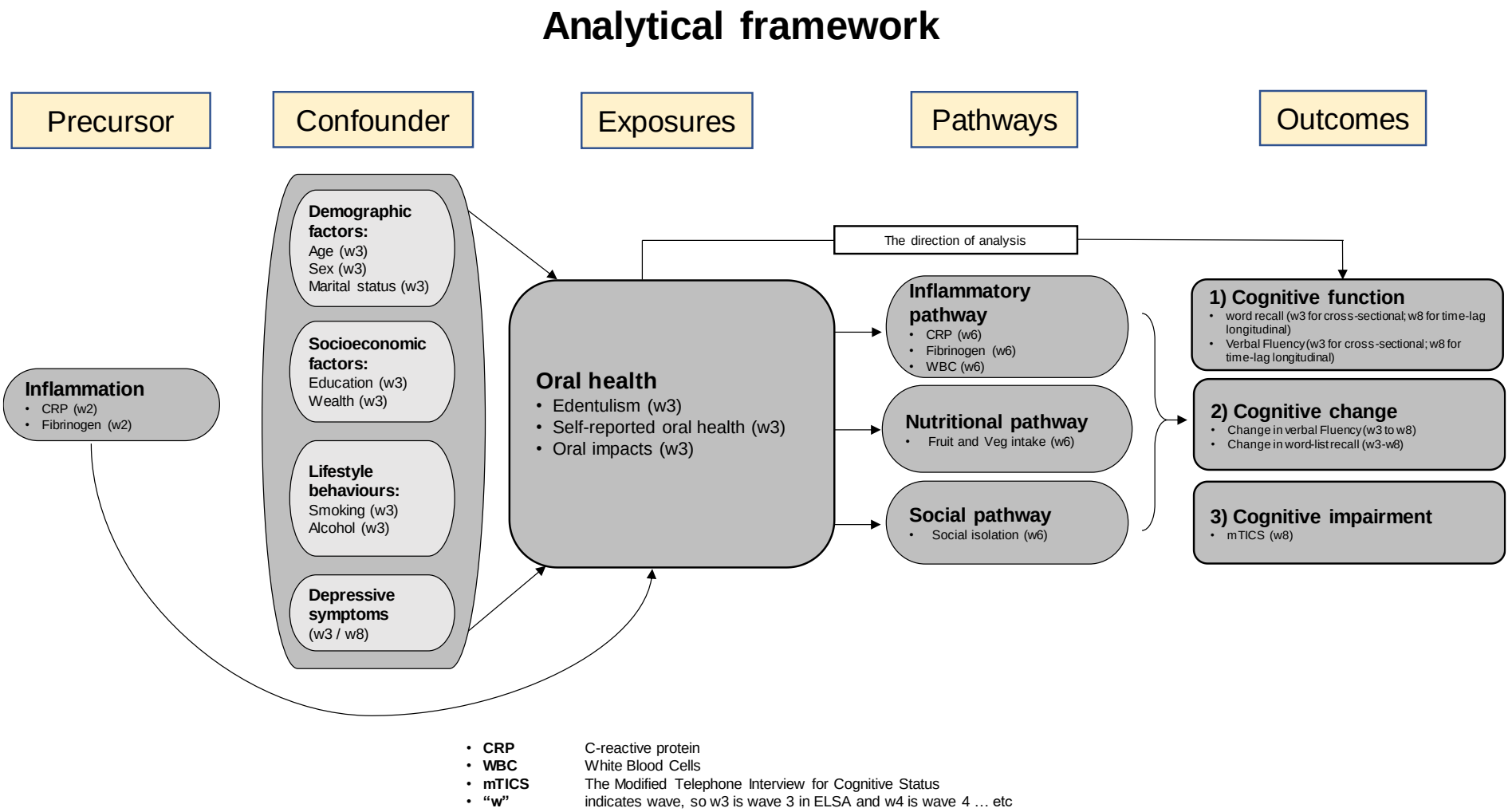

Figure 3.3 Conceptual analysis model of oral health and cognitive functioning, change and impairment

3.8.1 Cross-sectional analysis of the association between oral health and cognitive functioning (*Chapter 4*)

Objective 1

To investigate the cross-sectional association of different oral health measures (self-reported oral health, edentulism and oral impacts) with cognitive function (memory and executive function) at wave 3.

The multivariable associations between oral health exposures and cognitive function outcomes (memory and executive function) were examined using a series of *linear regression models*. Cognitive function outcomes were assessed by continuous variables (word-recall and animal naming tasks), and the trends between these scores and oral health measures were clearly linear. The normality was assessed for both memory and executive function, and they were not far from a normal distribution. Regression models were sequentially adjusted for *a priori* selected covariates (demographic, socio-economic, lifestyle behaviours and depressive symptoms). Initially, crude associations were examined by including only the main exposure variable into the linear regression model. Then, demographic variables were included in the model to control for the individual differences in cognitive function. The third model included additional controlling for socioeconomic variables. The fourth model included lifestyle behaviours (smoking status and alcohol consumption). The final model added depressive symptoms. The process of adjusting for covariates was as follows:

Model 1: unadjusted model;

Model 2: Model 1 with additional adjustment for age, sex and marital status;

Model 3: Model 2 additionally adjusting for education and wealth quintiles;

Model 4: Model 3 additionally adjusting smoking status and alcohol consumption;

Model 5: Model 4 additionally adjusting for depressive symptoms.

Furthermore, to investigate the effect modification of edentulism on the impact of self-reported oral health and oral impacts on cognitive functioning, the analytical sample was subcategorised into dentate and edentate groups according to the presence of teeth. Then, the same models mentioned earlier (models 1 to model 5) were used for both groups.

3.8.2 Longitudinal analysis of the impact of oral health on the subsequent cognitive function (*Chapter 5*)

Objective 2

To investigate the longitudinal associations of various oral health measures (self-reported oral health, edentulism and oral impacts) at waves 3 with cognitive function (memory and executive function) at wave 8.

The next step after the cross-sectional association was to assess the longitudinal associations between oral health at baseline and subsequent cognitive functioning. For that purpose, time-lag models were fitted as follows: the oral health predictor variables at wave 3 (2006-07) were related to the cognitive functioning outcome variables at wave 8 (2016-17), adjusted for covariates at wave 3 (2006-07) (models 1 to model 4), adjusted for depressive symptoms at the follow-up wave 8 (2016-17) (model 5). Time-lag models take into account the temporal sequence of a possible cause and effect. Additionally, autoregressive models were fitted by adjusting for the baseline outcome variable (Model 6). Autoregressive models help to “remove” the cross-sectional part of the relationships, in order to estimate the real influence of the predictor variables on the outcome variables (Twisk, 2013). The autoregressive models thus examined the association of oral health indicators at baseline with the change in cognitive function between waves 3 and 8. The process of adjusting for covariates was as follows:

Model 1: unadjusted model;

Model 2: Model 1 with additional adjustment for baseline age, sex and marital status;

Model 3: Model 2 additionally adjusting for baseline education and wealth quintiles;

Model 4: Model 3 additionally adjusting baseline smoking and alcohol;

Model 5: Model 4 additionally adjusting for wave 8 depressive symptoms;

Model 6: Model 5 additionally adjusting for the outcome at baseline.

The effect modification of edentulism on the impact of self-reported oral health and oral impacts on cognitive functioning was assessed. The analytical sample was subcategorised into dentate and edentate groups, and the associations were investigated in the same adjustment pattern mentioned earlier for each group.

3.8.3 Longitudinal analysis of the impact of oral health on the rate of change in cognitive function (*Chapter 6*)

Objective 3

To investigate the longitudinal associations of various oral health measures (self-reported oral health, edentulism and oral impacts) at waves 3 with the rate of change in cognitive function (memory and executive function) from wave 3 to wave 8.

In this chapter, *linear mixed-effects models* (Laird and Ware, 1982) were used to assess the longitudinal association between oral health at baseline and the change in cognitive performance over a 10-year period from wave 3 (2006-07) to wave 8 (2016-17). Figure 3.3 presents the structure of analyses and the basic concept of *linear mixed models* used in the study. The repeated measures at different waves of the same individual (level 1) were highly correlated with each other. The variation of cognition and oral health can differ by within and between individuals (level 2). *Linear mixed-effects model* is an optimal way to describe the change in continuous outcome variables over time and quantify its association with a range of exposure variables. It provides a flexible approach to take the intra-individual and inter-individual variation into account. It also allows for missing at random and unbalanced measurement intervals. A new continuous variable was created indicating the time of follow up since baseline (every 2 years). It was included to investigate the biannual rate of changes in cognitive function.

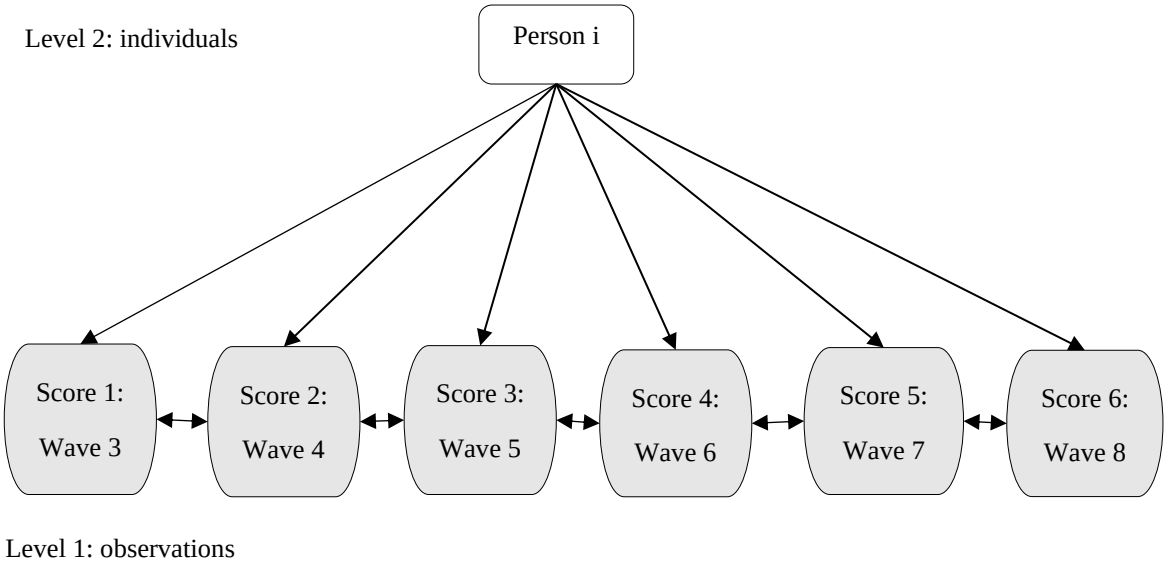

Figure 3.4 The structure of analyses in linear mixed model

In these models, both the intercept and the slope were fitted as random effects to account for interindividual differences at baseline and different rate of change of cognitive function over the follow-up. For the purpose of interpretation, age was centred at 70 years based on the mean age of the sample. The exposure oral health variables used at baseline were self-reported oral health (excellent, good and poor), edentulism (edentate vs dentate), oral impacts (having at least one impact vs none). The outcome variable was the change in cognitive performance scores from wave 3 to wave 8 measured by the immediate and delayed word recall test for memory and animal naming for executive function. Both, word-list recall and animal naming, were continuous variables and followed a linear structure over time. The following *linear mixed models* were fitted for each domain of cognitive function (memory and executive function):

Model 1: adjusted for time, baseline oral health variable and its interaction terms with time;

Model 2: model 1 additionally adjusted for baseline age-centred, sex, marital status and their interaction terms with time;

Model 3: model 2 additionally adjusted for baseline education and wealth and their interaction terms with time;

Model 4: model 3 additionally adjusted for baseline alcohol and smoking and their interaction terms with time;

Model 5: model 4 additionally adjusted for baseline depressive symptoms and its interaction term with time.

The *likelihood ratio test* was used to test the statistical significance between nested model to decide if adding more variables preferable over keeping the parsimonious model (Luke, 2017). The relative goodness of fit of the models is indicated by the log-likelihood, Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). The aim is to select the model with smaller log-likelihood, AIC and BIC.

3.8.4 Longitudinal analysis of the impact of oral health on subsequent cognitive impairment (*Chapter 7*)

Objective 4

To investigate the longitudinal associations of various oral health measures (self-reported oral health, edentulism and oral impacts) at wave 3 with the subsequent cognitive impairment at wave 8.

To assess the longitudinal associations between oral health at baseline and subsequent cognitive impairment, time-lag logistic regression models were fitted as follows: the oral health predictor variables at wave 3 (2006-07) were related to the binary cognitive impairment outcome variables at wave 8 (2016-17), adjusted for covariates at wave 3 (2006-07) (models 1 to model 4), adjusted for depressive symptoms at wave 8 (model 5). It was not possible to do the autoregressive models to remove the cross-sectional part of the relationships because the mTICS test battery used for cognitive impairment was included in ELSA at wave 7 for the first time. The process of adjusting for covariates was as follows:

Model 1: unadjusted model;

Model 2: Model 1 with additional adjustment for baseline age, sex and marital status;

Model 3: Model 2 additionally adjusting for baseline education and wealth quintiles;

Model 4: Model 3 additionally adjusting baseline smoking and alcohol;

Model 5: Model 4 additionally adjusting for wave 8 depressive symptoms.

The effect modification of edentulism on the impact of self-reported oral health and oral impacts on cognitive impairment was assessed, and the analytical sample was subcategorised into dentate and edentate groups. Then, the same models mentioned earlier (models 1 to model 5) were used for both groups.

3.8.5 Pathway analysis of the association between oral health and the subsequent cognitive impairment (*Chapter 8*)

Objective 5

To investigate the mediating factors (inflammatory, nutritional and social at wave 6) on the associations between oral health measures (self-reported oral health, edentulism and OIDP) at waves 3 and cognitive impairment (mTICS at wave 8).

The same sample for longitudinal studies (Sample 2) was used in this set of analysis. Two types of effects were presented: direct and indirect effects. The direct effect is the degree to which a change in a causal variable such as X produces a change in an effect variable such as Y variable without "going through" any other variable. Thus, the direct effect of X on M is represented by Path Coefficient a; the direct effect of M on Y is Path b; and the direct effect of X on Y is Path c. An indirect effect is the degree to which a change in a causal variable produces a change in an effect variable by means of an intervening variable overall indirect effect equals the sum of the product terms representing each of the routes (Maruyama, 1998; Cole and Maxwell, 2003). In Figure 3.4, X has an indirect effect on Y through M. Given that the variables are standardized, the indirect effect of X on Y through M is equal to the product of associated paths, a*b. In the current example, there is only one indirect effect; however, as presented in chapter 8, there is more than one potential route through intervening variables.

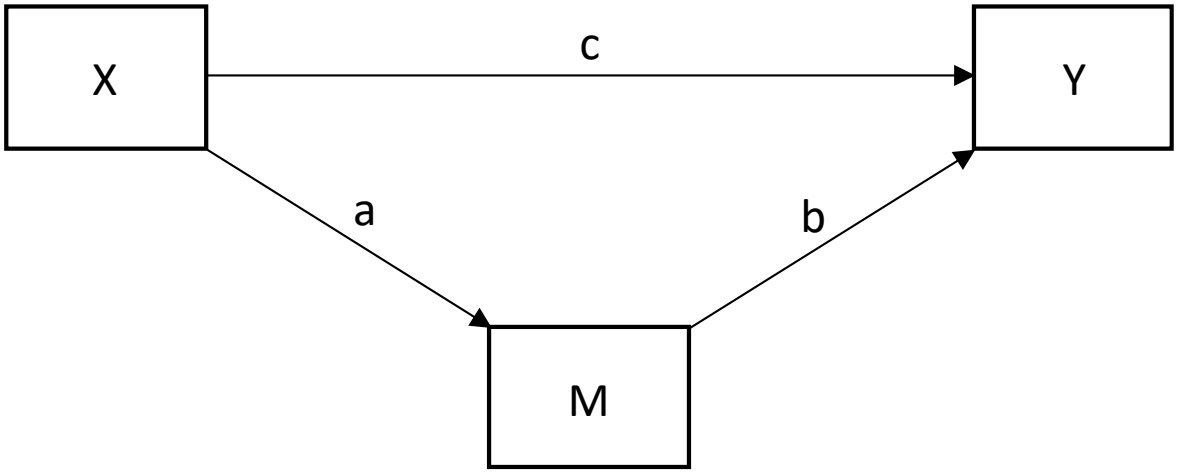

Figure 3.5 Illustration graph showing the difference between direct and indirect pathway

The three pathways assessed were inflammatory, social and nutritional pathway. Inflammatory markers (CRP, WBC and Fibrinogen) were used to create a single latent variable for inflammation. Social isolation and nutrition variables were explained previously in this chapter. Two sets of SEM models were created:
Model 1: unadjusted SEM model examining the association between oral health at wave 3 and cognitive impairment at wave 8 mediated by inflammation, social isolation and nutrition at wave 6;
Model 2: model 1 with additional adjustment of age and sex at wave 3.

The following four indices were utilized to evaluate the goodness of fit of the models: the standardized root mean square residual (SRMR); the root mean square error of approximation (RMSEA); the comparative fit index (CFI); and the Tucker-Lewis index (TLI). In this study, a model was considered to have a good fit if the SRMR and the RMSEA were below 0.08, the CFI and the TLI were 0.95 or more (Hooper et al., 2008).

Objective 6

To investigate the role of inflammation, assessed by inflammatory markers (CRP and fibrinogen) at wave 2, as a precursor in the associations between edentulism at wave 3 and cognitive impairment at wave 8.

Inflammation is expected to precede poor oral health. Therefore, in Chapter 8, inflammatory markers (CRP and Fibrinogen) at wave 2 were fitted in the SEM to assess their impact on the association between oral health at wave 3 and cognitive impairment at wave 8 mediated by social isolation and nutrition from wave 6.
Model 1: unadjusted SEM model examining the association between oral health at wave 3 and cognitive impairment at wave 8 mediated by social isolation and nutrition at wave 6 and preceded by inflammatory markers at wave 2.
Model 2: model 1 with additional adjustment of age and sex at wave 3.

THE CROSS-SECTIONAL ASSOCIATION OF ORAL HEALTH WITH COGNITIVE FUNCTIONING AT WAVE 3

4 THE CROSS-SECTIONAL ASSOCIATION OF ORAL HEALTH WITH COGNITIVE FUNCTIONING AT WAVE 3

The objective of this chapter was to investigate the cross-sectional association between oral health variables and different cognitive functioning measures (memory and executive function) (Figure 4.1). All oral health indicators were self-reported: self-reported oral health (excellent, good, and poor); edentulism (dentate vs edentate) and oral impacts (no impact vs at least one impact). The two cognitive functioning outcomes were memory and executive function. Memory function was assessed by the total score of the immediate and delayed word recall test, whereas executive functioning was assessed by the total number of animals named in one minute.

The hypothesis to be tested in this chapter was:

1. Poorer oral health measures are associated with lower levels of cognitive functioning independent of demographic and socioeconomic factors, lifestyle behaviours and depressive symptoms.

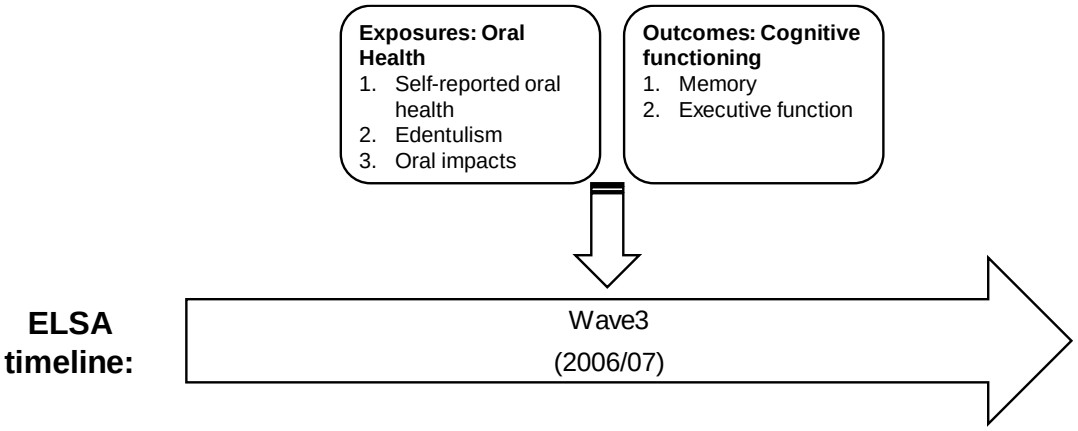

Figure 4.1 The analytical framework of the cross-sectional analysis of oral health and cognitive functioning at wave 3 (2006-07).

4.1 Eligible ELSA population sample and cross-sectional analytical sample

The analytical sample used in this thesis was a subset of ELSA data - wave 3 (2006-07). From the 9,771 wave 3 full sample, 961 were not core members; hence, they were excluded from the analytical sample (see Figure 4.2). This resulted in a sample of 8,810 respondents who were aged 50 and older. Of this sample, 7,535 (85.5%) were cohort 1 core members and 1,275 (14.5%) were cohort 3 core members. Cohort 1 core members are those from ELSA original sample, whereas cohort 3 core members are from the refreshment sample, which took place at wave 3.

Furthermore, participants diagnosed with any type of dementia were excluded from the sample (n=95). This resulted in an eligible sample of 8,715. Subsequently, 168 participants were excluded from the eligible sample because of missing data in the outcome variables -memory and executive function. Additionally, 5 participants were excluded because of missing data in the exposure variables (oral health measures) and 210 participants were excluded because of missing data some of the selected covariates. A total of 383 respondents were thus excluded, that is a decrease of 4.4% from the total eligible sample population.

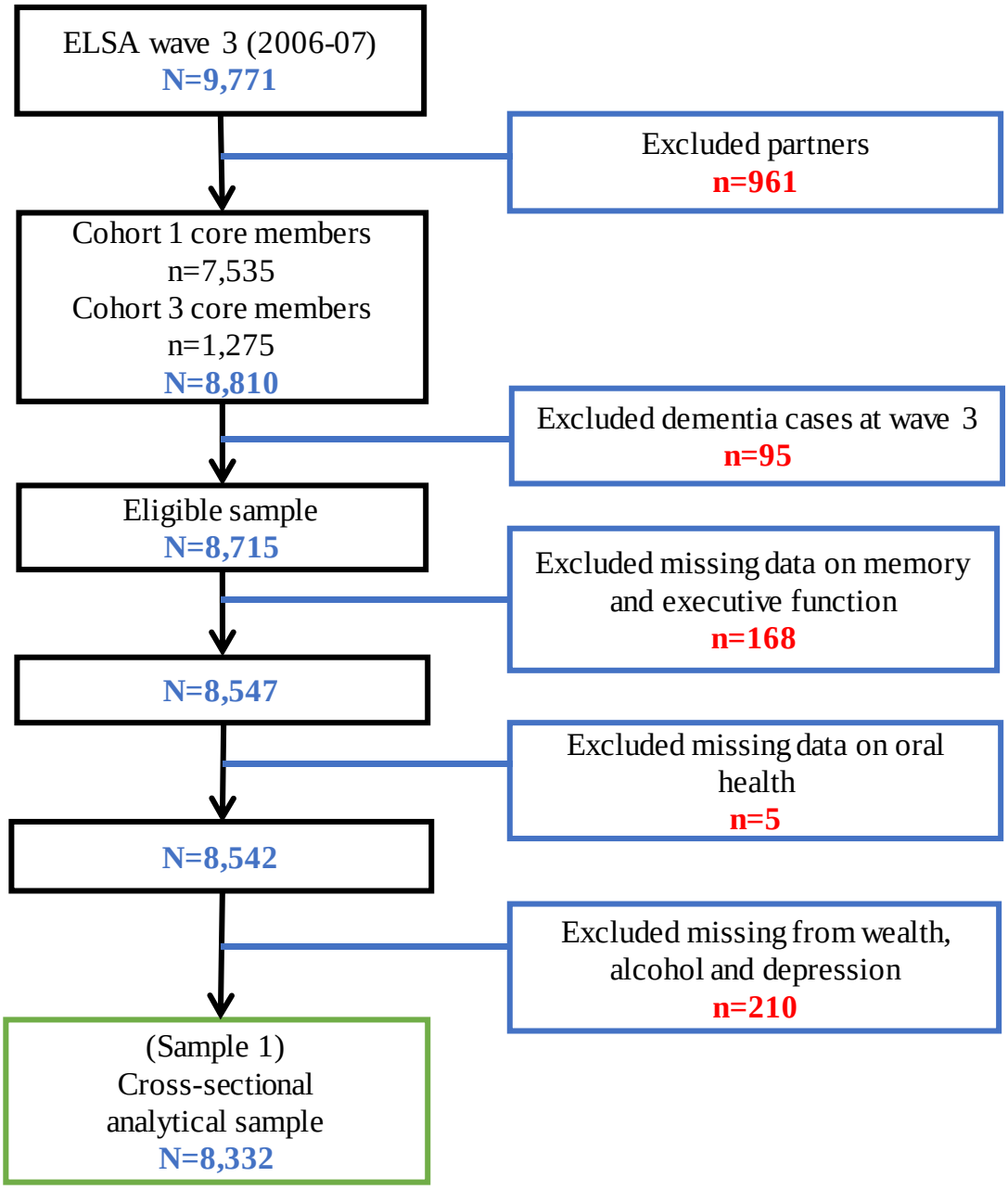

Figure 4.2 Flowchart of the analytical sample (N=8,332)

4.2 Results of the cross-sectional analysis

Data from 8,332 ELSA respondents constituted the sample for the baseline sample in this thesis. First, the characteristics of the baseline sample are presented in section 4.2.1. Then, section 4.2.2 presents the multivariable analysis of the association between oral health and memory. Finally, section 4.2.3 shows the multivariable analysis of the association between oral health and executive function, adjusted for covariates.

4.2.1 General characteristics of the baseline sample

As shown in Table 4.1, the average age of the sample was 65.8 years. The majority (43.4%) were aged between 50 and 64 years old, and almost a third of the sample (33.7%) were among the oldest group, 75 years or older. The proportion of female was slightly higher (55.2%) than males. The majority were married or cohabiting (67.8%), followed by 27.0% that were either widowed, divorced or separated. The sample had a slightly higher proportion of participants with an intermediate educational level. The median of the total net household wealth was £303,694. About 22.4% of the sample drank alcohol daily, and 14.7% reported being a current smoker. For depression, 14.9% reported having 4 or more depressive symptoms.

Table 4.1 General characteristics of ELSA wave 3 sample (N=8,332).

Characteristics	n (%)
Age	
Mean (SD) in years	65.80 (10.54)
50-64	4,236 (43.35)
65-74	2,238 (22.90)
>75	3,297 (33.74)
Sex	
Male	3,730 (44.77)
Female	4,602 (55.23)
Marital status	
Married or cohabiting	5,656 (67.88)
single, never married	426 (5.11)
widowed, divorced or separated	2,250 (27.01)
Education	
Higher qualification	2,670 (32.05)
Intermediate	3,207 (38.49)
No or low qualifications	2,455 (29.46)
Total net household wealth (Quintiles)	
Highest	1,494 (17.93)
4th	1,599 (19.19)
3rd	1,705 (20.46)
2nd	1,741 (20.90)
Lowest	1,793 (21.52)
Alcohol	
Less than daily	6,467 (77.62)
Daily	1,865 (22.38)
Smoking	
Never smoked	3,163 (37.96)
Previous smoker	3,944 (47.34)
Current smoker	1,225 (14.70)
Depressive symptoms	
No	7,088 (85.07)
Yes	1,244 (14.93)

4.2.1.1 Memory by general characteristics

As presented in Table 4.2, the average words recalled by the sample was 10.24 (standard deviation (SD)= 3.67). In this sample, older participants remembered, on average, fewer words than younger participants (*p*-value <0.001). The mean number of words recalled was slightly higher for females (mean 10.48, SD=3.72) compared to males (mean 9.94, SD=3.59, *p*-value <0.001). Participants who were married/cohabiting had higher average memory scores (mean 10.69, SD=3.46) compared to those who were single and never been married (mean 9.87, SD=3.91) and those who were widowed, divorced or separated (mean 9.17, SD=3.89, *p*-value <0.001). The highly educated participants had a better memory (mean 11.65, SD=3.36) compared to those who had intermediate education (mean 10.48, SD=3.40) or had low education (mean 8.39, SD=3.55, *p*-value <0.001). A similar pattern was observed for wealth; those who had higher wealth remembered more words in the memory test (mean 11.71, SD=3.29, *p*-value <0.001) than those in the lowest quintile. For alcohol, no major differences were found between those who drank daily compared to those who drank less frequently. Lastly, participants who reported fewer depressive symptoms recalled more words (mean 10.41, SD=3.61) compared to those who reported higher depressive symptoms(mean 9.24, SD=3.84, p-value <0.001).

4.2.1.2 Executive function by general characteristics

Similar trends to memory were observed for the executive function (Table 4.2). Older participants named fewer animals compared to their younger counterparts (*p*-value <0.001). Males named more animals (mean 20.58, SD= 6.88) compared to females (mean 19.82, SD= 6.69, *p*-value= 0.040). Married participants had a slightly better animal naming score (mean 20.93, SD=6.71) than those who were single and never been married (mean 19.39, SD=7.06) and those who were divorced, separated or widowed (mean 18.38, SD=6.56, *p*-value <0.001). Highly educated participants and those who were in the top wealth quintile had better executive function scores. Additionally, participants who reported drinking alcohol every day had better executive function score (mean 21.35, SD=6.75) than those who drank less often (mean 19.82, SD=6.76, *p*-value <0.001). The difference in animal naming between smoking groups was not significant (*p*-value = 0.503). For depressive symptoms, participants who reported higher depressive symptoms

named almost three animals less than those who reported less than four depressive symptoms (*p*-value <0.001).

Table 4.2 Characteristics of the sample (N=8,332) by memory and executive function at wave 3, mean (SD)

Characteristics	Memory Total mean (SD)= 10.24 (3.67)			Executive function Total mean (SD)= 20.16 (6.78)		
	mean (SD)		*p*-value [a]	mean (SD)		*p*-value [a]
Age						
50-64	11.53	(3.23)		21.97	(6.78)	
65-74	9.89	(3.33)		19.73	(6.28)	
>75	7.72	(3.60)	<0.001	16.55	(5.78)	<0.001
Sex						
Male	9.94	(3.59)		20.58	(6.88)	
Female	10.48	(3.72)	<0.001	19.82	(6.69)	0.040
Marital status						
Married or cohabiting	10.69	(3.46)		20.93	(6.71)	
single, never married	9.87	(3.91)		19.39	(7.06)	
widowed, divorced or separated	9.17	(3.89)	<0.001	18.38	(6.56)	<0.001
Education						
Higher qualification	11.65	(3.36)		22.80	(6.86)	
Intermediate	10.48	(3.40)		20.27	(6.38)	
No or low qualifications	8.39	(3.55)	<0.001	17.16	(5.95)	<0.001
Total net household wealth (Quintiles)						
Highest	11.71	(3.29)		22.62	(6.59)	
4th	10.81	(3.45)		20.90	(6.71)	
3rd	10.24	(3.65)		20.19	(6.70)	
2nd	9.72	(3.51)		19.40	(6.38)	
Lowest	8.72	(3.73)	<0.001	17.71	(6.55)	<0.001
Alcohol						
Less than daily	10.05	(3.65)		19.82	(6.76)	
Daily	10.89	(3.65)	<0.001	21.35	(6.75)	<0.001
Smoking						
Never smoked	10.51	(3.69)		20.36	(6.81)	
Previous smoker	10.11	(3.65)		20.19	(6.76)	
Current smoker	9.96	(3.65)	<0.001	19.56	(6.76)	0.503
Depressive symptoms						
No	10.41	(3.61)		20.53	(6.74)	
Yes	9.24	(3.84)	<0.001	18.06	(6.68)	<0.001

[a] P-values were calculated Kruskal–Wallis tests for ordinal covariates, and analysis of variance tests for other covariates

4.2.1.3 Self-reported oral health by general characteristics

Almost 43% of the sample reported excellent oral health, 39.5% reported good, and around 18% reported poor oral health (Table 4.3). Older groups reported less poor oral health than younger groups. Of those 75 years and older, 15.9% of participants reported poor oral health compared to 19.3% of the 50-64-year-old group. Males reported poorer oral health (19.2%), while married or cohabiting participants reported better oral health compared to other marital status groups. For education and wealth, those who were less educated and had the lowest level of wealth reported poorest oral health. Participants who drank on a daily basis reported more excellent and good oral health than those who reported drinking on a non-daily basis. Current and former smokers reported poorer oral health than those who never smoked. Lastly, those who reported higher depressive symptoms reported poorer oral health.

4.2.1.4 Edentulism by general characteristics

Edentate individuals were 10 years older on average than dentate (Table 4.4). Almost 37% of participants aged 75 years and older were edentate while only 6.3% of the 50-64 years old group were edentate. The percentage of female participants who were edentate was higher than for males, 18.6% and 14.5% respectively. Edentulism was more common in participants who were widowed, divorced or separated (28.5%), while only 12.2% of the married or cohabiting groups were edentate. For socioeconomic factors (education and wealth), almost a third of those who reported no education qualification or being in the lowest wealth quintile were edentate. Daily alcohol drinkers were less likely to be edentate than those who reported drinking less than daily. For smoking, a quarter (25%) of those who currently smoke was edentate compared to only 11% of those who never smoked. Participants who reported more depressive symptoms had more edentulism (22.8%).

4.2.1.5 Oral impacts by general characteristics

Younger participants (50-64 years old) reported fewer oral impacts than older participants (Table 4.4). There was no significant gender difference between different groups reporting oral impact. Widowed, divorced or separated participants reported more oral impacts (10.6%) than singles, never married (8.9%) or married and cohabiting participants (7.4%). Non-educated and participants in the lowest

wealth quintile reported more oral impacts than their counterparts. Participants who reported currently smoking and with higher depressive symptoms also reported higher oral impacts.

Table 4.3 Characteristics of the sample (N=8,332) by self-reported oral health at wave 3, n (%)

Characteristics	Self-reported oral health						*p-value* [a]
	Excellent n (%) = 3,556 (42.7)		**Good** 3,292 (39.5)		**Poor** 1,484 (17.8)		
Age							
Mean (SD) in years	66	(10.44)	66	(10.60)	65	(10.61)	
50-64	1,791	(42.28)	1,628	(38.43)	817	(19.29)	
65-74	960	(42.90)	906	(40.48)	372	(16.62)	
>75	805	(43.33)	758	(40.80)	295	(15.88)	<0.001
Sex							
Male	1,555	(41.69)	1,458	(39.09)	717	(19.22)	
Female	2,001	(43.48)	1,834	(39.85)	767	(16.67)	0.04
Marital status							
Married or cohabiting	2,506	(44.31)	2,232	(39.46)	918	(16.23)	
single, never married	160	(37.56)	169	(39.67)	97	(22.77)	
widowed, divorced or separated	890	(39.56)	891	(39.60)	469	(20.84)	<0.001
Education							
Higher qualification	1,251	(46.85)	1,008	(37.75)	411	(15.39)	
Intermediate	1,384	(43.16)	1,277	(39.82)	546	(17.03)	
No or low qualifications	921	(37.52)	1,007	(41.02)	527	(21.47)	<0.001
Total net household wealth (Quintiles)							
Highest	865	(48.24)	701	(39.10)	227	(12.66)	
4th	816	(46.87)	664	(38.14)	261	(14.99)	
3rd	727	(42.64)	711	(41.70)	267	(15.66)	
2nd	635	(39.71)	627	(39.21)	337	(21.08)	
Lowest	513	(34.34)	589	(39.42)	392	(26.24)	<0.001
Alcohol							
Less than daily	2,677	(41.39)	2,588	(40.02)	1,202	(18.59)	
Daily	879	(47.13)	704	(37.75)	282	(15.12)	<0.001
Smoking							
Never smoked	1,456	(46.03)	1,257	(39.74)	450	(14.23)	
Previous smoker	1,683	(42.67)	1,555	(39.43)	706	(17.90)	
Current smoker	417	(34.04)	480	(39.18)	328	(26.78)	<0.001
Depressive symptoms							
No	3,169	(44.71)	2,810	(39.64)	1,109	(15.65)	
Yes	387	(31.11)	482	(38.75)	375	(30.14)	<0.001

[a] P-values were calculated with analysis of variance test

Table 4.4 Characteristics of the sample (N=8,332) by edentulism and oral impacts at wave 3, n (%)

Characteristics	Edentulism					Oral Impacts				
	Dentate n (%) = 6,935 (83.2)		**Edentate** 1,397 (16.8)		***p-value*** [a]	**No impact** 7,634 (91.6)		**At least one impact** 698 (8.4)		***p-value*** [a]
Age										
Mean (SD) in years	64	(9.76)	74	(10.50)		66	(10.50)	67	(10.88)	
50-64	3,969	(93.70)	267	(6.30)		3,917	(92.47)	319	(7.53)	
65-74	1,808	(80.79)	430	(19.21)		2,029	(90.66)	209	(9.34)	
>75	1,158	(62.33)	700	(37.67)	<0.001	1,688	(90.85)	170	(9.15)	0.017
Sex										
Male	3,189	(85.50)	541	(14.50)		3,419	(91.66)	311	(8.34)	
Female	3,746	(81.40)	856	(18.60)	<0.001	4,215	(91.59)	387	(8.41)	0.907
Marital status										
Married or cohabiting	4,965	(87.78)	691	(12.22)		5,235	(92.56)	421	(7.44)	
single, never married	361	(84.74)	65	(15.26)		388	(91.08)	38	(8.92)	
widowed, divorced or separated	1,609	(71.51)	641	(28.49)	<0.001	2,011	(89.38)	239	(10.62)	<0.001
Education										
Higher qualification	2,477	(92.77)	193	(7.23)		2,490	(93.26)	180	(6.74)	
Intermediate	2,775	(86.53)	432	(13.47)		2,941	(91.71)	266	(8.29)	
No or low qualifications	1,683	(68.55)	772	(31.45)	<0.001	2,203	(89.74)	252	(10.26)	<0.001
Total net household wealth (Quintiles)										
Highest	1,707	(95.20)	86	(4.80)		1,697	(94.65)	96	(5.35)	
4th	1,569	(90.12)	172	(9.88)		1,610	(92.48)	131	(7.52)	
3rd	1,443	(84.63)	262	(15.37)		1,579	(92.61)	126	(7.39)	
2nd	1,223	(76.49)	376	(23.51)		1,447	(90.49)	152	(9.51)	
Lowest	993	(66.47)	501	(33.53)	<0.001	1,301	(87.08)	193	(12.92)	<0.001
Alcohol										
Less than daily	5,277	(81.60)	1,190	(18.40)		5,910	(91.39)	557	(8.61)	
Daily	1,658	(88.90)	207	(11.10)	<0.001	1,724	(92.44)	141	(7.56)	0.148
Smoking										
Never smoked	2,799	(88.49)	364	(11.51)		2,964	(93.71)	199	(6.29)	
Previous smoker	3,218	(81.59)	726	(18.41)		3,611	(91.56)	333	(8.44)	
Current smoker	918	(74.94)	307	(25.06)	<0.001	1,059	(86.45)	166	(13.55)	<0.001
Depressive symptoms										
No	5,975	(84.30)	1,113	(15.70)		6,610	(93.26)	478	(6.74)	
Yes	960	(77.17)	284	(22.83)	<0.001	1,024	(82.32)	220	(17.68)	<0.001

[a] P-values were calculated with analysis of variance test

4.2.1.6 The bivariate association of memory and executive function by oral health variables

4.2.1.6.1 Memory by oral health

The results of bivariate analyses of different oral health variables with memory function are shown in Table 4.5. Participants who reported excellent oral health remembered on average 10.46 words (SD=3.64) compared to only 9.90 words (SD=3.69, p-value <0.001) for those who reported poor oral health. For edentulism, dentate participants on average, remembered 10.66 words (SD= 3.64) compared to only 8.16 words (SD=3.74) for edentate participants (p-value <0.001). Lastly, participants who reported at least one oral impact remembered slightly fewer words (mean=10.29, SD=3.66) than those who reported no oral impacts (mean 9.66, SD =3.72, p-value <0.001).

4.2.1.6.2 Executive function by oral health

For self-reported oral health (Table 4.5), participants who reported poor oral health named slightly fewer animals than other groups with a mean of 19.35 (SD=7.03, p-value <0.001). Moreover, dentate participants named 20.8 (SD=6.77) animals; while edentate participants named on average 16.9 (SD=5.92) animals (p-value <0.001). For the oral impacts, participants who reported no oral impact named more animals (mean 20, SD =6.78) than those who reported none (mean 18.9, SD =6.71, p-value <0.001).

Table 4.5 Summary of cognitive functioning score by oral health of the analytical sample (N=8,332), mean (SD)

	Self-reported oral health				**Edentulism**			**Oral Impacts**		
	Excellent	**Good**	**Poor**	***P-value***	**Dentate**	**Edentate**	***P-value***	**No impact**	**At least one impact**	***P-value***
Memory	10.46 (3.64)	10.15 (3.68)	9.90 (3.69)	<0.001	10.66 (3.51)	8.16 (3.74)	<0.001	10.29 (3.66)	9.66 (3.72)	<0.001
Executive function	20.61 (6.71)	20.04 (6.72)	19.35 (7.03)	<0.001	20.81 (6.77)	16.96 (5.92)	<0.001	20.00 (6.78)	18.92 (6.71)	<0.001

p-value *<0.05, ** <0.01, ***<0.001

4.2.2 The multivariable regression analyses of oral health and memory

In the previous section, the bivariate analyses of the associations between oral health and memory were presented. In this section, the associations will be examined by multivariable regression analyses adjusting for potential covariates. Overall, the results showed that poor oral health was associated with lower memory (Table 4.6). However, socioeconomic factors, in addition to demographic factors, attenuated this association considerably. Details of these association are explained in this section.

4.2.2.1 Self-reported oral health and memory

The linear regression analysis showed that self-reported oral health was significantly associated with memory in the unadjusted model (Model1, Table 4.6). Participants who reported poor (β= -0.56, 95% CI: -0.78, -0.34) and good oral health (β= -0.30, 95%CI: -0.48, -0.13) remembered significantly fewer words compared to those who reported excellent oral health. Controlling for age, sex and marital status (Model 2, Table 4.6) contributed to minimal changes in the estimates. Further adjustment for socioeconomic factors considerably attenuated the estimates for those who reported good and poor oral health. The difference between those reporting excellent and those reporting good oral health was not significant at this stage (β= -0.11, 95%CI: -0.26, 0.04) and remained so for the further stages of adjustment. Adjusting for socioeconomic factors also resulted in considerably reduced differences between those with excellent and those with poor oral health. However, the difference was still significant (β= –22, 95%CI: -0.42, -0.03). Including lifestyle behaviours to the model did not result in any considerable changes to the estimates. Finally, adding depressive symptoms in the final model (Model 5, Table 4.6) attenuated the difference between those reporting excellent and those reporting poor oral health considerably and became non-significant in this stage.

When the sample was stratified into dentate and edentate groups, the association remained almost the same for dentate participants but got strengthened in the edentate group (Table 4.7). In the unadjusted model, the differences between those reporting excellent and those reporting good oral health were higher in edentate participants (β= -0.57, 95%CI: -1.00, -0.15) compared to dentate participants (β= -0.30, 95%CI: -0.48, -0.12). Similarly, the differences between

those reporting excellent and those reporting poor oral health were considerably higher in edentate participants (β= -1.13, 95%CI: -1.71, -0.55) compared to dentate participants (β= -0.58, 95%CI: -0.81, -0.35). In both groups, demographic factors attenuated the association. Moreover, adjusting for the socioeconomic factors considerably attenuated the association in both groups. Further adjustment of lifestyle behaviours slightly attenuated the associations in both dentate and edentate participants. Finally, controlling for depressive symptoms in the fully adjusted model substantially attenuated the association; yet remained significant only among edentate participants. In summary, stratifying the sample according to edentulism, showed stronger estimates for the associations between self-reported oral health and memory in edentate participants. The association between poor oral health in edentates participants and memory was significant in the fully adjusted model (β= -0.61, 95%CI: -1.13,-0.08), whereas depressive symptoms explained the association for the whole sample and dentate participants.

4.2.2.2 Edentulism and memory

The cross-sectional association between memory and edentulism was stronger than with the self-reported oral health or with oral impacts (Table 4.6). In the unadjusted model, the memory function of edentate participants was significantly lower than dentate (β= -2.50, 95%CI: -2.71, -2.30). Controlling for socio-demographic factors attenuated the association considerably in model 2 (β= -1.27, 95% CI: -1.48, -1.07). Further adjustment for socioeconomic factors continued to reduce the differences in memory scores between dentate and edentate (β= -0.58, 95% CI: -0.78, -0.38). Moreover, introducing lifestyle behaviours in model 4 and depressive symptoms in model 5 did not influence the association considerably. In the final model, edentate participants remembered significantly fewer words than dentate (β= -0.57, 95% CI: -0.77, -0.37).

4.2.2.3 Oral impacts and memory

The cross-sectional association between memory and oral impacts was weaker than the association of edentulism with memory (Table 4.6). In the crude model, the difference between those who reported at least one oral impact and those who reported none was significant (β= -0.63, 95% CI: -0.92, -0.35); however, it got slightly attenuated after controlling for demographic factors in model 2 (β= -

0.44, 95% CI: -0.70, -0.19). Further adjustment of socioeconomic factors in model 3 attenuated and the difference and became non-significant. Further adjustment for lifestyle behaviours and depressive symptoms contributed to an additional attenuation in the difference; although it was not significant in these models.

Stratifying the analysis by edentulism showed a stronger association between oral impacts and memory in the unadjusted model for dentate participants (β= -0.53, 95% CI: -0.83, -0.22) (Table 4.7). Controlling for demographic factors attenuated the association for dentate participants (β= -0.34, 95% CI: -0.62, -0.06) and considerably strengthened the association for edentate participants (β= -0.59, 95% CI: -1.17, -0.02). The socioeconomic factors attenuated the association for dentate participants and became non-significant (β= -0.17, 95% CI: -0.45, 0.10) and slightly attenuated the association for edentate participants but remained significant (β= -0.57, 95% CI: -1.13, -0.02). Further adjustment for lifestyle behaviours had a minimum effect on the associations. Nonetheless, including depressive symptoms in the final model had a substantial effect attenuating the associations on both groups, dentate and edentate participants. As a result, the association between oral impacts and memory for the edentate participants became non-significant in the fully adjusted model (β= -0.39, 95% CI: -0.95, 0.17).

Table 4.6 The cross-sectional association between oral health and memory at wave 3 of ELSA (N=8,332), results from the linear regression, β (95% CI)

Outcome: Memory	**Model 1** (Unadjusted)		**Model 2** (Model 1 +age, sex & marital status)		**Model 3** (Model 2 + education & wealth)		**Model 4** (Model 3+ smoking & alcohol)		**Model 5** (Model 4 + depressive symptoms)	
Self-reported oral health										
Excellent (ref)										
Good	-0.30***	(-0.48, -0.13)	-0.26**	(-0.42, -0.10)	-0.11	(-0.26,0.04)	-0.10	(-0.25,0.05)	-0.08	(-0.23, 0.07)
poor	-0.56***	(-0.78, -0.34)	-0.60***	(-0.80, -0.40)	-0.22*	(-0.42, -0.03)	-0.20*	(-0.40, -0.01)	-0.11	(-0.30, 0.08)
Edentulism										
Dentate (ref)										
Edentate	-2.50***	(-2.71, -2.30)	-1.27***	(-1.48, -1.07)	-0.58***	(-0.78, -0.38)	-0.56***	(-0.76, -0.36)	-0.57***	(-0.77, -0.37)
Oral impacts										
No impact (ref)										
At least one impact	-0.63***	(-0.92, -0.35)	-0.44***	(-0.70, -0.19)	-0.19	(-0.43, 0.06)	-0.17	(-0.42, 0.07)	-0.05	(-0.30, 0.20)

p-value *<0.05, ** <0.01, ***<0.001

Table 4.7 The cross-sectional association of self-reported oral health and oral impacts with memory at wave 3 for dentate and edentate participants, results from the linear regression (N=8,332), β (95% CI)

Outcome: Memory	**Model 1** (Unadjusted)		**Model 2** (M1 +age, sex & marital status)		**Model 3** (M2 + education & wealth)		**Model 4** (M3+ smoking & alcohol)		**Model 5** (M4 + depressive symptoms)	
Dentate (n=6,935)										
Self-reported oral health										
Excellent (ref)										
Good	-0.30**	(-0.48, -0.12)	-0.22*	(-0.38,-0.05)	-0.09	(-0.25,0.08)	-0.07	(-0.23,0.09)	-0.04	(-0.20,0.12)
Poor	-0.58***	(-0.81, -0.35)	-0.57***	(-0.78,-0.36)	-0.29**	(-0.49,-0.08)	-0.24*	(-0.44,-0.03)	-0.13	(-0.34,0.08)
Oral impacts										
No impact (ref)										
At least one impact	-0.53***	(-0.83, -0.22)	-0.34*	(-0.62,-0.06)	-0.17	(-0.45,0.10)	-0.14	(-0.41,0.13)	0.01	(-0.26,0.29)
Edentate (n=1,397)										
Self-reported oral health										
Excellent (ref)										
Good	-0.57**	(-1.00, -0.15)	-0.49*	(-0.87,-0.10)	-0.38*	(-0.76,-0.01)	-0.35	(-0.72,0.03)	-0.3	(-0.67,0.08)
Poor	-1.13***	(-1.71, -0.55)	-1.11***	(-1.64,-0.58)	-0.84**	(-1.35,-0.32)	-0.79**	(-1.30,-0.27)	-0.61*	(-1.13,-0.08)
Oral impacts										
No impact (ref)										
At least one impact	-0.41	(-1.05,0.22)	-0.59*	(-1.17,-0.02)	-0.57*	(-1.13,-0.02)	-0.56*	(-1.12,-0.01)	-0.39	(-0.95,0.17)

p-value *<0.05, ** <0.01, ***<0.001

4.2.3 The multivariable regression analyses of oral health and executive function

The associations between oral health indicators and executive function were stronger than the associations with memory. Edentate participants and those who reported poor oral health at wave 3 had a lower executive function, measured by animal naming, independent of all covariates. This section will explain in detail the cross-sectional associations between oral health variables and executive function.

4.2.3.1 Self-reported oral health and executive function

In general, participants who reported poorer oral health named fewer animals than those who reported excellent oral health (see Table 4.8). There was a clear gradient association with worse executive function for each group with worse self-reported oral health in the unadjusted model. Likewise, Introducing demographic factors in model 2 showed similar association gradient; the poorer oral health, the lower executive function. In model 3, further adjustment of socioeconomic factors substantially attenuated the association. In this model, the difference in executive function between those who reported excellent and those who reported good oral health had become non-significant (β= -0.27, 95% CI: -0.56, 0.02) and stayed so for the further stages of adjustment. The differences in executive function between those in excellent and those in poor oral health groups were considerably smaller but remained significant (β= -0.77, 95% CI: -1.15, -0.39). Moreover, further controlling for lifestyle behaviours had no impact on the estimates (or the significance) of associations between self-reported oral health and executive function.

In contrast, further adjustment for depressive symptoms in the fully adjusted model resulted in further attenuation; however, the difference in executive function between those in excellent and those in poor self-reported oral health remained significant (β= -0.58, 95% CI: -0.96, -0.20).

The effect modification of edentulism in the association between executive function and self-rated oral health showed a stronger association among the edentate group (Table 4.9). In the fully adjusted model, edentate participants who reported poor oral health had significantly lower memory (β= -1.55, 95%CI: -0.99, -0.15); compared to dentate participants who reported poor oral health (β= -0.57, 95%CI: -2.42, -0.68).

Stratifying the analysis between dentate and edentate confirmed the pattern of changes throughout the adjustment process seen for the whole sample analysis. However, throughout this process, the estimates for the edentate were considerably higher than those for the dentate, and this was also reflected in the fully adjusted models. The differences in executive function scores between those reporting excellent and those reporting poor oral health were substantially higher in edentate participants (β= -1.55, 95%CI: -2.42, -0.68) compared to dentate participants (β= -0.57, 95%CI: -0.99, -0.15).

4.2.3.2 Edentulism and executive function

The cross-sectional association between executive function and edentulism was strong (Table 4.8). The unadjusted model showed that edentate named fewer animals than dentate (β= -3.84, 95% CI: -4.22, -3.46). This estimate was considerably attenuated by controlling for demographic factors (β= -2.03, 95% CI: -2.42, -1.64). Additionally, adjusting for socioeconomic factors continued attenuating the association considerably (β= -0.93, 95% CI: -1.32, -0.54). Further adjusting for lifestyle behaviours and depressive symptoms did not have a considerable effect on the association. In the fully adjusted model, edentate participants had significantly worse executive function than the dentate (β= -0.92, 95% CI: -1.31, -0.53).

4.2.3.3 Oral impacts and executive function

For oral impacts, the unadjusted model showed that participants who reported at least one oral impact named significantly fewer words than those who reported no oral impact (β= -1.35, 95% CI: -1.88, -0.82) (Model 1, Table 4.8). Adjusting for demographic factors attenuated the association in model 2 (β= -1.08, 95% CI: -1.58, -0.58). Introducing socioeconomic factors attenuated that association substantially in model 3 (β= -0.67, 95% CI: -1.14, -0.19). Adjusting for lifestyle behaviours had no impact on the association. In contrast, further adjustment for depressive symptoms attenuated the association considerably and explained it (β= -0.42, 95% CI: -0.58, 0.06).

Stratifying the analysis between dentate and edentate showed a stronger association among the dentate group in the unadjusted model (Model 1, Table 4.9). Adjusting for demographic factors attenuated the association among dentate group (β= -0.97, 95%CI: -1.54, -0.40) and strengthened the association among edentate

group (β= -1.06, 95%CI: -2.01, -0.11). On the other hand, the socioeconomic factors attenuated the association substantially among the dentate group (β= -0.68, 95%CI: -1.23, -0.13), and had a very slight effect on the edentate group (β= -1.02, 95%CI: -1.95, -0.10). The adjustment of lifestyle behaviours had no considerable effect on both groups. Finally, adjusting depressive symptoms resulted in a substantial attenuation among both groups and the associations became non-significant for the edentate participants.

Table 4.8 Association between oral health and executive function at wave 3, results of linear regression (N=8,332), β (95% CI)

Outcome: Executive Function	**Model 1** (Unadjusted)		**Model 2** (Model 1 +age, sex & marital status)		**Model 3** (Model 2 + education & wealth)		**Model 4** (Model 4+ smoking & alcohol)		**Model 5** (Model 4 + depressive symptoms)	
Self-reported oral health										
Excellent (ref)										
Good	-0.56***	(-0.88, -0.24)	-0.51**	(-0.81, -0.20)	-0.27	(-0.56, 0.02)	-0.26	(-0.55, 0.04)	-0.21	(-0.50, 0.09)
poor	-1.25***	(-1.66, -0.84)	-1.37***	(-1.76, -0.98)	-0.77***	(-1.15, -0.39)	-0.75***	(-1.13, -0.37)	-0.58**	(-0.96, -0.20)
Edentulism										
Dentate (ref)										
Edentate	-3.84***	(-4.22, -3.46)	-2.03***	(-2.42, -1.64)	-0.93***	(-1.32, -0.54)	-0.91***	(-1.30, -0.52)	-0.92***	(-1.31, -0.53)
Oral impacts										
No impact (ref)										
At least one impact	-1.35***	(-1.88, -0.82)	-1.08***	(-1.58, -0.58)	-0.67**	(-1.14, -0.19)	-0.65**	(-1.13, -0.17)	-0.42	(-0.91, 0.06)

p-value *<0.05, ** <0.01, ***<0.001

Table 4.9 The cross-sectional association of self-reported oral health and oral impacts with executive function at wave 3 for dentate and edentate, results of linear regression (N=8,332), β (95% CI)

Outcome: Executive function	**Model 1** (Unadjusted)		**Model 2** (M1 +age, sex & marital status)		**Model 3** (M2 + education & wealth)		**Model 4** (M3+ smoking & alcohol)		**Model 5** (M4 + depressive symptoms)	
Dentate (n=6,935)										
Self-reported oral health										
Excellent (ref)										
Good	-0.52**	(-0.87,-0.17)	-0.40*	(-0.74,-0.06)	-0.17	(-0.50,0.15)	-0.15	(-0.48,0.17)	-0.1	(-0.43,0.22)
poor	-1.26***	(-1.71,-0.82)	-1.29***	(-1.72,-0.87)	-0.81***	(-1.22,-0.39)	-0.75***	(-1.17,-0.33)	-0.57**	(-0.99,-0.15)
Oral impacts										
No impact (ref)										
At least one impact	-1.24***	(-1.83,-0.66)	-0.97***	(-1.54,-0.40)	-0.68*	(-1.23,-0.13)	-0.63*	(-1.18,-0.08)	-0.38	(-0.93,0.18)
Edentate (n=1,397)										
Self-reported oral health										
Excellent (ref)										
Good	-1.13***	(-1.80,-0.46)	-1.05**	(-1.68,-0.42)	-0.91**	(-1.53,-0.29)	-0.86**	(-1.48,-0.24)	-0.76*	(-1.39,-0.14)
poor	-2.23***	(-3.15,-1.31)	-2.31***	(-3.18,-1.44)	-1.96***	(-2.82,-1.10)	-1.90***	(-2.76,-1.04)	-1.55***	(-2.42,-0.68)
Oral impacts										
No impact (ref)										
At least one impact	-0.81	(-1.81,0.19)	-1.06*	(-2.01,-0.11)	-1.02*	(-1.95,-0.10)	-1.01*	(-1.93,-0.08)	-0.66	(-1.59,0.27)

p-value *<0.05, ** <0.01, ***<0.001

Summary

The analyses of this chapter presented some evidence of a significant cross-sectional association between oral health and cognitive functioning. The unadjusted model showed that those who reported good or poor oral health remembered fewer words (β= -0.30, 95%CI: -0.48, -0.13 and β= -0.56, 95%CI: -0.78, -0.34, respectively) than those who reported excellent oral health. The differences in memory between good oral health and excellent oral health became non-significant after adjusting for socioeconomic factors (β= -0.11, 95%CI: -0.26, 0.04), while the differences between poor oral health and excellent oral health became non-significant after adjusting for depressive symptoms (β= -0.11, 95%CI: -0.30, 0.08). Stratifying the analysis between dentate and edentate showed considerably stronger estimates among edentate participants. In the fully adjusted model, the differences in memory function between those who reported poor oral health and those who reported excellent oral health were significant (β= -0.61, 95%CI: -1.13, -0.08). A similar pattern of changes, which was observed in memory, was also found for executive function. Those who reported poorer oral health had the worst executive function. The unadjusted findings after stratifying the sample into dentate and edentate showed larger memory function differences between good/poor oral health and excellent oral health among edentate participants compared to dentate participants. The difference in memory remained significant in the fully adjusted model for good and poor compared to excellent oral health (β= -0.76, 95%CI: -1.39, -0.14 and β= -1.55, 95%CI: -2.42, -0.68, respectively).

For edentulism, edentate participants remembered fewer words and named fewer animals than dentate participants in the fully adjusted model (β= -0.57, 95%CI: -0.77, -0.37 and β= -0.92, 95%CI: -1.31, -0.53, respectively). Both were heavily attenuated by demographic and socioeconomic factors but remained significant in the fully adjusted models.

For oral impacts, the difference in memory function between those who reported at least one oral impacts and those who reported none was significant in the unadjusted model (β= -0.63, 95%CI: -0.92, -0.35), and remained significant until the adjustment for socioeconomic factors, where it became non-significant (β= -0.19, 95%CI: -0.43, 0.06). The difference in executive function between those who reported at least one oral impacts and those who reported none was strong (β= -1.35, 95%CI: -1.88, -0.82, for the unadjusted model), and remained significant until

the model adjusted for depressive symptoms (β= -0.42, 95%CI: -0.91, 0.06). Stratifying the analysis between dentate and edentate showed larger differences in both cognitive domains (memory and executive function) between those who reported at least one oral impacts and those who reported none in the edentate group compared to the dentate group. However, none of the estimates for the oral impacts was significant in the fully adjusted model.

THE LONGITUDINAL ASSOCIATION BETWEEN ORAL HEALTH AT WAVE 3 AND COGNITIVE FUNCTIONING AT WAVE 8

5 THE LONGITUDINAL ASSOCIATION BETWEEN ORAL HEALTH AT WAVE 3 AND COGNITIVE FUNCTIONING AT WAVE 8

In the previous chapter (Chapter 4), the cross-sectional analysis between oral health and cognitive functioning at wave 3 was presented. The results showed that edentate participants remembered fewer words than dentate participants after controlling for potential covariates. Likewise, those who reported poor oral health remembered fewer words than those who reported excellent oral health, yet that association was explained by additionally controlling for depressive symptoms. Furthermore, controlling for socioeconomic factors explained the association between oral impacts and memory. For the executive function, edentate participants or those who had poor oral health named fewer animals than their counterparts after controlling for an array of covariates. In the fully adjusted model, depressive symptoms explained the association between oral impacts and executive function. Stratifying the sample into dentate and dentate showed stronger associations of edentate participants who reported poor oral health or reported at least one oral impact with lower memory scores.

In this chapter, the longitudinal association between oral health and cognitive performance will be investigated with the assumption that poorer oral health measures at baseline (wave 3) are associated with subsequent lower cognitive performance, measured by memory and executive function, 10 years later (Figure 5.1).

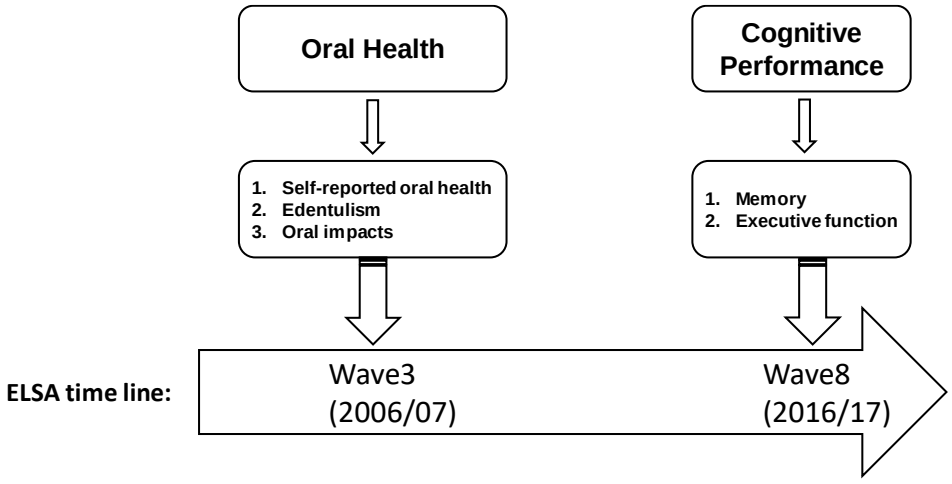

Figure 5.1 The analytical framework of oral health at wave 3 and cognitive functioning at wave 8

The key hypothesis to be tested in this chapter is:

- Poor oral health measures (self-reported oral health, edentulism and oral impacts) at baseline (wave 3, 2006-07) will be associated with lower cognitive functioning (memory and executive function) 10 years later (wave 8, 2016-17) independent of covariates adjustment.

To assess the longitudinal associations between oral health and cognitive functioning, *time-lag linear regression* models were employed. First, the unadjusted association between oral health exposure variables at wave 3 and cognitive functioning outcome variables at wave 8 was tested; secondly, the model was adjusted for demographic factors (age, sex and marital status), socioeconomic factors (education and wealth) and lifestyle behaviours (smoking and alcohol) at wave 3 (Model 2 to Model 4), followed by the adjustment to depressive symptoms at wave 8 (Model 5) and the outcome variables at wave 3 (Model 6). In model 6, the autoregressive association was fitted to the model to account for the cross-sectional effect and get a better estimate on longitudinal models (Twisk, 2013).

This chapter is structured as follows: Section 5.1 presents the description of the longitudinal analytical sample, including missingness from wave 3 to wave 8; section 5.2 presents the longitudinal estimates of the association between oral health at wave 3 and memory performance at wave 8, and finally, section 5.3 presents the findings from the association between oral health at wave 3 and executive performance at wave 8.

5.1 Analytical sample

The ELSA baseline sample (described in detail in the previous chapter) at wave 3 (2006-07) was 8,332. At first, new cases of dementia, Alzheimer's or Parkinson's disease were excluded from the sample. Then, individuals who did not participate in the follow-up wave 8 were excluded from the sample. There were 492 cases from the baseline sample who died in the period from wave 3 to wave 8, 772 were alive but did not participate in wave 8, and for 1,268 participants it was not known whether they were alive or dead by the time of collecting the data for wave 8 Additionally, 873 cases were excluded because of missing data in the outcome of interest at wave 8. Then, 213 cases were excluded because of missing data for variable on depressive symptoms. Therefore, the final sample size for this set of analyses was 3,856 (Figure 5.2).

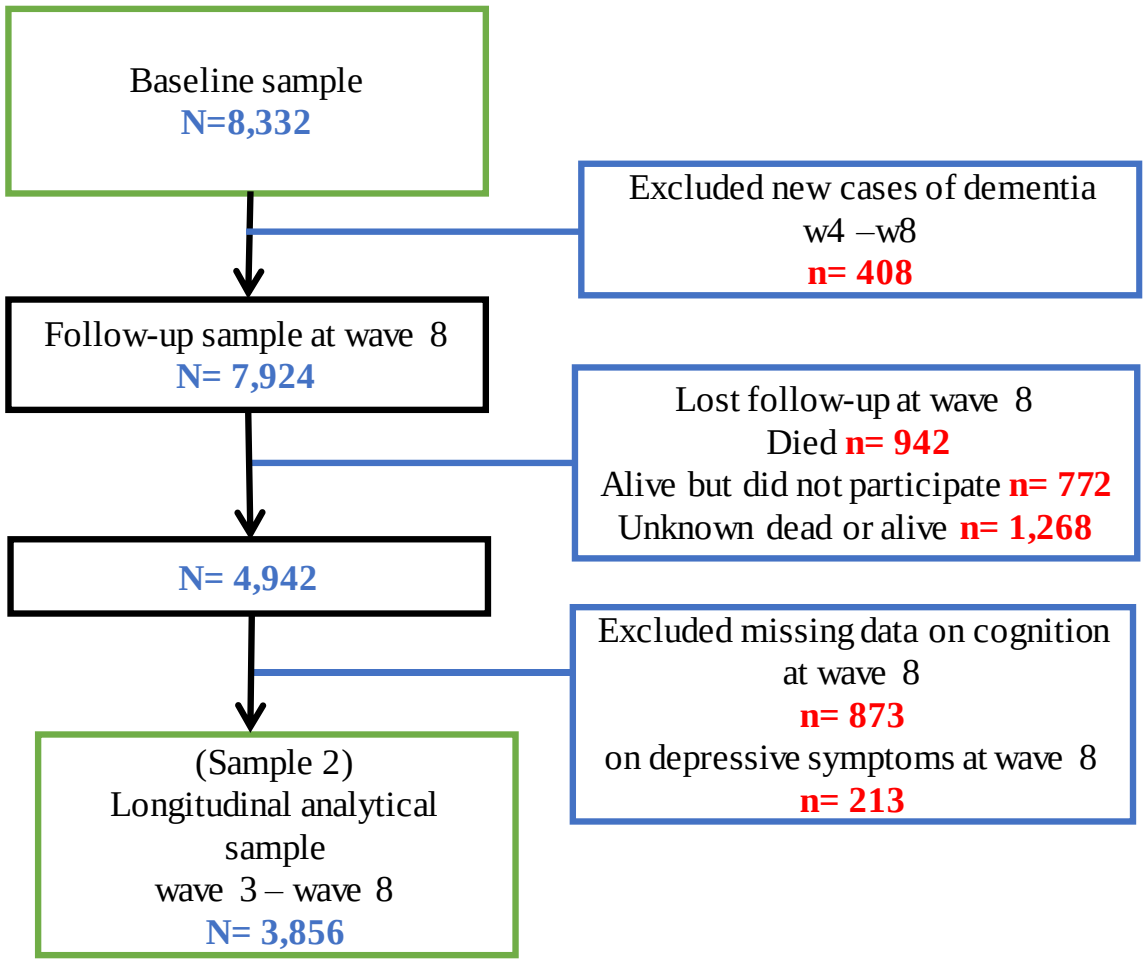

Figure 5.2 Flowchart of the analytical sample (N=3,856)

5.2 Oral health at wave 3 and memory at wave 8

5.2.1 Self-reported oral health and memory

The time-lag linear regression analysis showed that people who reported poorer oral health at wave 3 had poorer memory 10 years later at wave 8 (Table 5.1). In the unadjusted model (Model 1), those who reported poor oral health at wave 3 remembered fewer words than those who reported excellent oral health (β= -0.27, 95% CI: -0.60, 0.05, p-value > 0.05). Likewise, those who reported good oral health remembered fewer words than those who reported excellent oral health (β= -0.19, 95% CI: -0.44, 0.06, p-value > 0.05). However, the unadjusted associations were not significant. Further adjustment of demographic factors, particularly age, strengthened the association, and these became significant. In a supplementary analysis, participants who reported poor oral health had lower memory function (β= -0.50, 95% CI: -0.80, -0.20, *p*-value= 0.001) adjusted for age. In model 3, including socioeconomic factors (education and wealth) attenuated the association substantially, and this then became non-significant. Further adjustment of lifestyle behaviours (smoking and alcohol) and depressive symptoms at wave 8 attenuated the associations. In the autoregressive model (Model 6), the associations strengthened slightly but remained non-significant.

The effect modification by edentulism in the association between memory and self-reported oral health showed a stronger association among edentate participants (Table 5.2). Controlling for demographic factors strengthened the associations among both groups, dentate and edentate, but to a greater extent for edentate participants. Further controlling for socioeconomic factors resulted in a considerable attenuation, which was more profound in the dentate group. Controlling for smoking and alcohol attenuated the association among the dentate group and strengthened the association among the edentate group. Likewise, controlling for depressive symptoms at wave 8, in model 5, attenuated the association substantially among the dentate group, while controlling the same variable among edentate participants strengthened the association. Edentate participants who reported good oral health at wave 3 had significantly lower memory in the fully adjusted model (Model 6) (β= -0.92, 95%CI: -1.65, -0.19); while among dentate participants, the association was not significant (β= -0.08, 95%CI: -0.29, 0.13). Although the association was significant in the full model among the

edentate group, controlling for memory at wave 3 attenuated the association considerably. Controlling for memory at wave 3 in model 6 (the autoregressive model) had a greater impact on edentate participants than on dentate participants.

5.2.2 Edentulism and memory

The association of edentulism at wave 3 with memory at wave 8 was very strong (Table 5.1). Edentate participants remembered fewer words than dentate participants in the unadjusted model (β= -2.27, 95% CI: -2.66, -1.89). In model 2, adjusting for demographic factors attenuated 46% of the association (β= -1.22, 95% CI: -1.58, -0.85). Furthermore, adjusting for social factors (education and wealth) was responsible for a further 45% attenuation of the association (β= -0.67, 95% CI: -1.03, -0.31). Moreover, further adjusting for smoking, alcohol and depression had a slight impact on the association. Finally, in the last model, where memory at wave 3 was added to the analysis (the auto-regressive model), the association was further attenuated but remained significant (β= -0.48, 95% CI: -0.81, -0.15). Almost 20% of the association was attenuated by controlling for memory at wave 3. However, the association remained significant in the fully adjusted model.

5.2.3 Oral impacts and memory

For oral impacts, the association with memory at wave 8 was weaker than for edentulism with memory (Table 5.1). In the crude model (Model 1), those who reported at least one oral impact remembered fewer words than those who reported no oral impact (β= -0.69, 95% CI: -1.12, -0.26). The adjustment of demographic factors in model 2 attenuated the association slightly (β= -0.60, 95% CI: -0.99, -0.20), and a considerable further attenuation of this association was observed as a result of a further adjustment of socioeconomic factors (wealth and education) (β= -0.40, 95% CI: -0.78, -0.03). Then, the adjustment for smoking and alcohol in model 4 slightly attenuated the association and became not significant (β= -0.38, 95% CI: -0.76, -0.00). Further adjusting for depression (Model 5) attenuated the already non-significant association (β= -0.22, 95% CI: -0.60, 0.16). Finally, the association remained non-significant in the autoregressive model (β= -0.24, 95% CI: -0.59, 0.11).

Further analysis of stratified samples by edentulism showed different trends between dentate and edentate groups (Table 5.2). The association got attenuated in both groups, although it was significant among dentate (β= -0.55, 95% CI: -1.01, -0.10) and non-significant among edentate (β= -0.53, 95% CI: -1.76, 0.69). Adjusting for demographic factors attenuated the association among dentate group (β= -0.45, 95% CI: -0.87, -0.03) and strengthened the association among edentate group (β= -1.05, 95% CI: -2.16, 0.07). The socioeconomic factors, when they were added to the mode, attenuated the association substantially and explained it among dentate participants (β= -0.29, 95% CI: -0.70, 0.11), and to a less extent among edentate participants (β= -0.92, 95% CI: -2.01, 0.16). Lifestyle behaviours showed an opposite impact on both groups; they attenuated the association slightly among dentate participants and strengthened the association among edentate participants, including depressive symptoms in model 5 resulted in a considerable attenuation among both groups. Finally, controlling for memory at wave 3 in model 6 resulted in a considerable attenuation in the association among the dentate group; however, controlling for the same variable among edentate group strengthened the association.

Table 5.1 Linear regression of the longitudinal association between oral health at wave 3 and memory at wave 8 (n=3,856), β (95% CI)

Outcome: Memory	**Model 1** (Unadjusted)		**Model 2** (Model 1 + age, sex & marital status)		**Model 3** (Model 2 + education & wealth)		**Model 4** (Model 3+ smoking & alcohol)		**Model 5** (Model 4 + depressive symptoms)		**Model 6** (Model 5 + memory at wave 3)	
Self-reported oral health												
Excellent (ref)												
Good	-0.19	(-0.44, 0.06)	-0.27*	(-0.50, -0.04)	-0.16	(-0.37, 0.06)	-0.14	(-0.36, 0.08)	-0.12	(-0.33, 0.10)	-0.14	(-0.34, 0.06)
Poor	-0.27	(-0.60, 0.05)	-0.42**	(-0.72, -0.12)	-0.16	(-0.45, 0.12)	-0.13	(-0.42, 0.16)	-0.03	(-0.32, 0.26)	-0.04	(-0.31, 0.23)
Edentulism												
Dentate (ref)												
Edentate	-2.27***	(-2.66, -1.89)	-1.22***	(-1.58, -0.85)	-0.67***	(-1.03, -0.31)	-0.63***	(-0.99, -0.27)	-0.60**	(-0.96, -0.24)	-0.48**	(-0.81, -0.15)
Oral impacts												
No impact (ref)												
At least one impact	-0.69**	(-1.12, -0.26)	-0.60**	(-0.99, -0.20)	-0.40*	(-0.78, -0.03)	-0.38	(-0.76, 0.00)	-0.22	(-0.60, 0.16)	-0.24	(-0.59, 0.11)

p-value *<0.05, ** <0.01, ***<0.001

Table 5.2 Time-lag and autoregressive linear regression analysis of self-reported oral health and oral impacts at wave 3 with memory at wave 8 for dentate and edentate, β (95% CI)

Outcome: memory	**Model 1** (Unadjusted)		**Model 2** (M1 +age, sex & marital status)		**Model 3** (M2 + education & wealth)		**Model 4** (M3+ smoking & alcohol)		**Model 5** (M4 + depressive symptoms)		**Model 6** (M5 + memory at wave 3)	
Dentate (n=3,501)												
Self-reported oral health												
Excellent (ref)												
Good	-0.19	(-0.44, 0.06)	-0.20	(-0.44, 0.03)	-0.10	(-0.33, 0.12)	-0.09	(-0.31, 0.14)	-0.05	(-0.27, 0.18)	-0.08	(-0.29, 0.13)
Poor	-0.35*	(-0.68, -0.02)	-0.38*	(-0.69, -0.08)	-0.13	(-0.43, 0.16)	-0.1	(-0.39, 0.20)	0.00	(-0.30, 0.30)	-0.01	(-0.29, 0.26)
Oral impacts												
No impact (ref)												
At least one impact	-0.55*	(-1.01, -0.10)	-0.45*	(-0.87, -0.03)	-0.29	(-0.70, 0.11)	-0.27	(-0.68, 0.13)	-0.13	(-0.54, 0.27)	-0.20	(-0.57, 0.17)
Edentate (n=355)												
Self-reported oral health												
Excellent (ref)												
Good	-0.76	(-1.63, 0.11)	-1.15**	(-1.93, -0.36)	-0.92*	(-1.69, -0.14)	-0.95*	(-1.74, -0.16)	-1.04**	(-1.83, -0.25)	-0.92*	(-1.65, -0.19)
Poor	-0.32	(-1.57, 0.93)	-1.32*	(-2.46, -0.18)	-0.98	(-2.11, 0.16)	-1.03	(-2.18, 0.12)	-0.92	(-2.07, 0.22)	-0.76	(-1.82, 0.30)
Oral impacts												
No impact (ref)												
At least one impact	-0.53	(-1.76, 0.69)	-1.05	(-2.16, 0.07)	-0.92	(-2.01, 0.16)	-0.96	(-2.06, 0.14)	-0.75	(-1.87, 0.36)	-0.46	(-1.50, 0.57)

p-value *<0.05, ** <0.01, ***<0.001

5.3 Oral health at wave 3 and executive function at wave 8

5.3.1 Self-reported health and executive function

The analysis showed a non-significant negative association between self-reported oral health at wave 3 and executive function at wave 8 (Table 5.3). The crude model showed that participants who reported good oral health had a lower executive function at wave 8 (β= -0.16, 95% CI: -0.64, 0.32) and poor oral health (β= -0.21, 95% CI: -0.84, 0.42) compared to excellent oral health at wave 3. Adding demographic factors to model 2 made the association stronger between poor (β= -0.28, 95% CI: -0.74, 0.18) and good oral health and executive function (β= -0.46, 95% CI: -1.06, 0.15). Adjusting for socioeconomic factors substantially attenuated the association between self-reported oral health and executive function. Further attenuation of the association took place after controlling for smoking and alcohol in model 4. Moreover, depressive symptoms slightly attenuated the association. Finally, controlling for executive function at wave 3 slightly attenuated the association and remained non-significant in the fully adjusted model.

Looking at the difference between dentate and edentate groups, the association slightly got stronger but remained non-significant through all models (Table 5.4). Adjusting for demographics strengthened the associations among both groups, but in a larger extent among edentate participants. Adding education and wealth resulted in a considerable attenuation in the associations among both groups. Further adjustment of lifestyle behaviours and depressive symptoms attenuated the associations to some extent in both groups. An additional attenuation was the result of a further adjustment of the outcome of interest at baseline among both groups, dentate and edentate (Model 6, Table 5.4).

5.3.2 Edentulism and executive function

Similar to the association with memory, the association of edentulism at wave 3 with the executive function at wave 8 was very strong (Table 5.3). Those who reported being edentate remembered fewer words than dentate participants in the unadjusted model (β= -3.61, 95% CI: -4.35, -2.86). However, 42% of that association attenuated after adjusting for demographic factors (β= -2.07, 95% CI: -2.81, -1.33). Moreover, further adjustment for education and wealth in model 3 substantially attenuated the association (β= -1.09, 95% CI: -1.83, -0.35).

Additionally, including lifestyle factors (alcohol and smoking) and depressive symptoms slightly attenuated the association. Lastly, in the autoregressive model (model 6), the association got slightly attenuated but remained significant (β= -0.95, 95% CI: -1.61, -0.28).

5.3.3 Oral impacts and executive function

As shown in other oral health variables, participants who reported at least one oral impact at wave 3 had worse executive function score (β= -0.97, 95% CI: -1.80, -0.14) (Table 5.3). Adjusting for socioeconomic factors attenuated the association in model 2 (β= -0.81, 95% CI: -1.61, -0.01). The socioeconomic factors substantially attenuated the association as shown in model 3, (β= -0.46, 95% CI: -1.24, 0.32), and became non-significant in this model and across the rest of models. Adding lifestyle behaviours to the model slightly attenuated the association (β= -0.42, 95% CI: -1.20, 0.35). Further adjustment of depressive symptoms attenuated the association (β= -0.20, 95% CI: -0.98, 0.58). Finally, in the autoregressive model (model 6), adding executive function at wave 3 to the analysis have attenuated the association (β= -0.09, 95% CI: -0.97, 0.61).

In another set of analysis that looked at dentate and edentate groups separately (Table 5.4), the association got slightly attenuated among dentate participants (β= -0.49, 95% CI: -1.37, 0.38) and, in the opposite, got substantially strengthened among edentate group (β= -2.23, 95% CI: -4.71, 0.25). Adjusting for demographics attenuated the association among dentate participants (β= -0.33, 95% CI: -1.18, 0.52) and strengthened the association among edentate participants (β= -2.76, 95% CI: -5.18, -0.34). Moreover, including socioeconomic factors substantially attenuated the association among dentate group (β= 0.06, 95% CI: -0.88, 0.77) and slightly attenuated the association among dentate group (β= -2.57, 95% CI: -4.94, -0.20). Further adjustment of lifestyle behaviours and depressive symptoms slightly attenuated the associations. Finally, controlling for executive function at wave 3 in the autoregressive models slightly attenuated the association among dentate participants (β= 0.33, 95% CI: -0.40, 1.07) and strengthened the association among edentate participants (β= -2.27, 95% CI: -4.65, 0.10).

Table 5.3 Linear regression of the longitudinal association between oral health at wave 3 and executive function (animal naming) at wave 8 (n=3,856), β (95% CI)

Outcome: Executive function	**Model 1** (Unadjusted)		**Model 2** (Model 1 +age, sex & marital status)		**Model 3** (Model 2 + education & wealth)		**Model 4** (Model 3+ smoking & alcohol)		**Model 5** (Model 4 + depressive symptoms)		**Model 6** (Model 5 + executive function at wave 3)	
Self-reported oral health												
Excellent (ref)												
Good	-0.16	(-0.64, 0.32)	-0.28	(-0.74, 0.18)	-0.08	(-0.52, 0.37)	-0.05	(-0.50, 0.39)	-0.02	(-0.46, 0.43)	0.06	(-0.34, 0.46)
Poor	-0.21	(-0.84, 0.42)	-0.46	(-1.06, 0.15)	0.04	(-0.55, 0.64)	0.09	(-0.50, 0.69)	0.23	(-0.37, 0.82)	0.42	(-0.11, 0.95)
Edentulism												
Dentate (ref)												
Edentate	-3.61***	(-4.35, -2.86)	-2.07***	(-2.81, -1.33)	-1.09**	(-1.83, -0.35)	-1.05**	(-1.79, -0.30)	-1.01**	(-1.75, -0.27)	-0.95**	(-1.61, -0.28)
Oral impacts												
No impact (ref)												
At least one impact	-0.97*	(-1.80, -0.14)	-0.81*	(-1.61, -0.01)	-0.46	(-1.24, 0.32)	-0.42	(-1.20, 0.35)	-0.20	(-0.98, 0.58)	-0.09	(-0.79, 0.61)

p-value *<0.05, ** <0.01, ***<0.001

Table 5.4 Time-lag and autoregressive linear regression analysis of self-reported oral health and oral impacts at wave 3 with executive function at wave 8 for dentate and edentate, β (95% CI)

Outcome: Executive function	**Model 1** (Unadjusted)		**Model 2** (M1 +age, sex & marital status)		**Model 3** (M2 + education & wealth)		**Model 4** (M3+ smoking & alcohol)		**Model 5** (M4 + depressive symptoms)		**Model 6** (M5 + executive function at wave 3)	
Dentate (n=3,501)												
Self-reported oral health												
Excellent (ref)												
Good	-0.25	(-0.73, 0.24)	-0.28	(-0.75, 0.19)	-0.1	(-0.56, 0.36)	-0.08	(-0.54, 0.38)	-0.02	(-0.48, 0.44)	0.04	(-0.36, 0.45)
Poor	-0.26	(-0.90, 0.38)	-0.35	(-0.97, 0.27)	0.11	(-0.50, 0.72)	0.15	(-0.46, 0.76)	0.3	(-0.31, 0.91)	0.49	(-0.05, 1.03)
Oral impacts												
No impact (ref)												
At least one impact	-0.49	(-1.37, 0.38)	-0.33	(-1.18, 0.52)	-0.06	(-0.88, 0.77)	-0.03	(-0.85, 0.80)	0.19	(-0.63, 1.02)	0.33	(-0.40, 1.07)
Edentate (n=355)												
Self-reported oral health												
Excellent (ref)												
Good	-0.19	(-1.97, 1.58)	-0.51	(-2.25, 1.22)	0.06	(-1.65, 1.77)	0.42	(-1.31, 2.14)	0.38	(-1.35, 2.11)	0.5	(-1.21, 2.20)
Poor	-1.29	(-3.83, 1.26)	-2.35	(-4.87, 0.16)	-1.38	(-3.88, 1.12)	-0.95	(-3.46, 1.56)	-0.9	(-3.42, 1.62)	-0.7	(-3.17, 1.78)
Oral impacts												
No impact (ref)												
At least one impact	-2.23	(-4.71, 0.25)	-2.76*	(-5.18, -0.34)	-2.57*	(-4.94, -0.20)	-2.2	(-4.59, 0.18)	-2.13	(-4.56, 0.29)	-2.27	(-4.65, 0.10)

p-value *<0.05, ** <0.01, ***<0.001

Summary

Overall, in this prospective analysis over 10 years, poorer oral health at wave 3 was associated with lower cognitive functioning at wave 8. For self-reported oral health, the associations were non-significant, in the fully adjusted model, except between good oral health and memory among edentate participants. Adjusting for demographic factor strengthened the association with both outcomes. Strengthening the association was greater among edentate participants. Socioeconomic factors had the most attenuating impact on the associations between self-reported oral health and cognitive functioning.

Overall, the association of edentulism with the executive function was stronger than the association with memory. Edentulism was the strongest oral health indicator in this chapter for both outcomes. Nevertheless, the associations got attenuated substantially (almost 70%), in both outcomes, by demographic and socioeconomic factors. Controlling for memory and executive functions at wave 3 in the full models was a response for further attenuation of the association between edentulism at wave 3 and cognitive functioning at wave 8.

For the oral impacts, the overall association with memory was stronger than the association with executive functioning. Controlling for demographics attenuated the association with both outcomes of cognitive function, except the associations among edentate groups.

THE LONGITUDINAL ASSOCIATION BETWEEN ORAL HEALTH AND CHANGE IN COGNITIVE FUNCTIONING

6 THE LONGITUDINAL ASSOCIATION BETWEEN ORAL HEALTH AND THE RATE OF CHANGE IN COGNITIVE FUNCTIONING

In the previous chapter, the prospective association between oral health and cognition was presented using the *time-lag* and the *autoregressive linear regression* models. These analyses confirmed a significant negative relationship between oral health and cognitive performance. Participants who reported being edentate at wave 3 recalled fewer words and named fewer animals 10 years later at wave 8, compared to dentate participants and controlling for many covariates. There was no statistically significant association of self-reported oral health neither with memory nor with executive function. For oral impacts, participants who reported at least one oral impact at wave 3 remembered fewer words and named fewer animals at wave 8, although the association with memory was explained by further adjusting for lifestyle behaviours and the association with the executive function was explained by further adjusting for socioeconomic factors. All previous chapters assessed the associations between oral health at baseline and the outcome at one time of point, either cross-sectionally at wave 3 (Chapter 4) or longitudinally at wave 8 (Chapter 5). This chapter will examine the longitudinal association between oral health at baseline and the rate of change in cognitive performance over a 10-year period from wave 3 to wave 8 employing *Linear Mixed-effects Models* (Figure 6.1).

In these analyses, oral health measures at baseline were self-reported oral health (excellent, good and poor), edentulism (edentate vs dentate), oral impacts (having at least one impact vs none). The outcome variable was the rate of change in cognitive performance from wave 3 to wave 8 measured specifically by word recall test for memory and animal naming for executive function. Models were sequentially adjusted for baseline covariates as follows:

Model 1: Adjusted for time, baseline oral health variable and its interaction terms with time;

Model 2: model 1 additionally adjusted for baseline age, sex, marital status and their interaction terms with time;

Model 3: model 2 additionally adjusted for baseline education and wealth and their interaction terms with time;

Model 4: model 3 additionally adjusted for baseline alcohol and smoking and their interaction terms with time;

Model 5: model 4 additionally adjusted for baseline depressive symptoms and its interaction term with time.

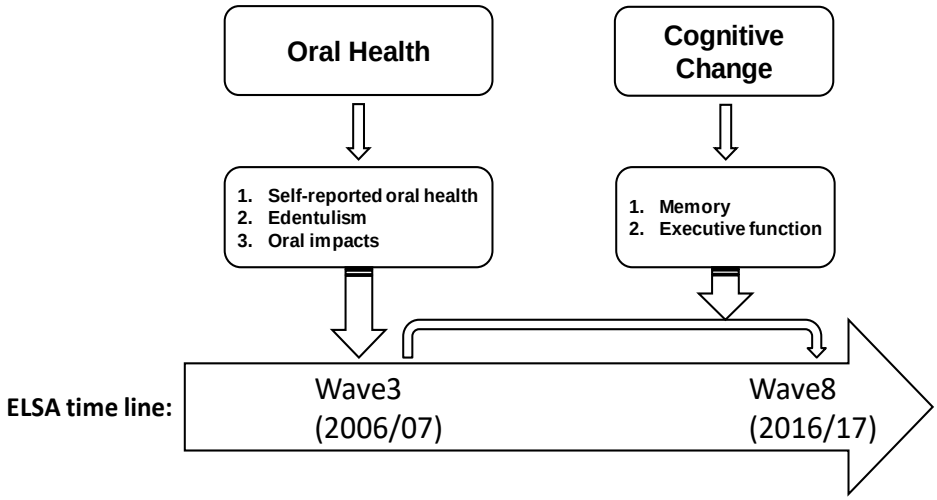

Figure 6.1 The analytical framework of the longitudinal association between oral health at wave 3 and change in cognitive functioning from wave 3 to wave 8

Oral health measures and other covariates were time-invariant in these analyses and only accounted for at baseline. Age was centred to the mean to make the interpretation of the results meaningful. *Linear Mixed-effects Models (Laird and Ware, 1982)* were analysed to assess the changes in cognitive functioning (continuous scores of word recall test and animal naming) over time and quantify their association with a range of exposure variables. It provides a flexible approach to take the intra-individual and inter-individual variation into account. It also allows for missing at random and unbalanced measurement intervals (Fitzmaurice and Ravichandran, 2008). Time was created as a new continuous variable representing the biannual rate of changes in cognitive function.

6.1 Comparing linear and quadratic models

This section compares models that included only linear slopes (time, covariates and their interaction with time) to models that also included additional quadratic slopes ($time^2$ and the covariates interaction with $time^2$). Table 6.1 summarises the results of the Bayesian Information Criteria (BIC), which is the index that will be used to select the best model. Lower BIC value indicates lower penalty terms hence a better model. As shown in Table 6.1, the models included only linear slopes, for both memory and executive function had the lowest BIC compared to quadratic models. Therefore, the linear models were selected to be presented in this chapter.

Table 6.1 The BIC results comparing linear to quadratic models

	Linear model "BIC"	Quadratic model "BIC"
Outcome: Memory		
Self-reported oral health	164933.4	165061.9
Edentulism	164894.1	165012.5
Oral impacts	164910.1	165029.1
Outcome: Executive Function		
Self-reported oral health	178176.7	178299.9
Edentulism	178142.1	178261.8
Oral impacts	178159	178282.7

6.2 Oral health and change in memory

This section describes the results from the *Linear-mixed models* to show the longitudinal association between different oral health variables and the rate of change in memory from wave 3 to wave 8. The outputs of the *mixed-effects models*, as shown in Tables 6.2 to 6.7, contain different sections. The first section of tables 6.2 to 6.7 under the headline "*the estimates at baseline"* presents the cognitive function intercepts at each model and the effect of oral health and other covariates on intercepts of cognitive functioning. The second section of tables 6.2 to 6.7 shows the central part for this chapter under the headline "*the estimate of the rate of change"*. This section presents the rate of cognitive function change over time and the impact of oral health measures in addition to other covariates on the rate of cognitive functioning change. Then, the group-level slope and intercept variances and the relationship between them (the covariance) will be presented in tables 6.2 to 6.7. Finally, at the bottom of each table, the goodness of fit measures will be presented: the log-likelihood, the Akaike information criterion (AIC), the Bayesian Information Criteria (BIC), and the p-value of the likelihood ratio test.

6.2.1 Self-reported oral health and the rate of change in memory

Overall, self-reported oral health was not significantly associated with the rate of memory change over time (Table 6.2). Participants who reported good oral health at wave 3, had faster memory decline in the fully adjusted model (β= -0.02, 95% CI: -0.06, 0.02), yet that association was not significant.

In model 1, the average words recalled at baseline was 10.85 (95% CI: 10.74, 10.96) controlling for time, self-reported oral health and its interaction with time. Memory, in model 1, significantly decline from wave 3 to wave 8 (β= -0.20, 95% CI: -0.22, -0.17). As previously mentioned, the effects of good (β= -0.02, 95% CI: -0.06, 0.02) and poor (β= -0.02, 95% CI: -0.03, 0.07) oral health on the rate of

memory change were not significant. The group-level slope and intercepts variances in this model were 0.13 and 7.13. The covariance was positive (0.18), which suggests that participants with higher memory at baseline had lower slopes, and those who had lower baseline memory had a steeper decline.

In model 2, the impact of self-reported oral health on the rate of memory change was not significant and did not have any considerable changes from the previous model. The rate of memory change over time became positive in this model (β= 0.11, 95% CI: 0.05, 0.17). For the effect of age on the rate of change, for every year increase in age, memory significantly declined (β= -0.02, 95% CI: -0.02, -0.02). The group-level slope and intercepts variances in this model were reduced by adjusting for demographics and their interactions with time, 0.10 and 5.23, respectively.

In model 3, after further controlling for education, wealth and their interactions with time, the association between self-reported oral health and the rate of memory change did not have any considerable change in this model. Likewise, the rate of memory change overtime remained significant and did not change. Those who were among the middle wealth group (3rd quintile) had significantly steeper memory decline after adjusting for several covariates in this model (β= -0.06, 95% CI: -0.11, -0.01).

In model 4, after further controlling for lifestyle behaviours (alcohol and smoking), their interactions with time slightly attenuated the association of poor oral health and memory at baseline (β= -0.20, 95% CI: -0.38, -0.02). The rate of change in memory over time and the association between self-reported oral health and the rate of memory change had no considerable change in this model.

Lastly, controlling for depressive symptoms at model 5 increased the memory at baseline slightly (β= 9.24, 95% CI: 8.91, 9.56). The association between poor oral health and memory at baseline was attenuated and became non-significant (β= -0.12, 95% CI: -0.31, 0.06). The rate of memory change over time and the association between self-reported oral health and the rate of memory change did not change in this model. The impact of age on the rate of memory change remained significant (β= -0.02, 95% CI: -0.02, -0.02). Likewise, the association of middle wealth class and memory change remained significant (β= -0.07, 95% CI: -0.12, -0.01).

Table 6.2 The results from linear mixed models of self- reported oral health at wave 3 on memory change over 10 years. (n=6,998), β (95% CI)

Outcome: Memory change (wave 3 - wave 8)	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
Intercept Mean (95% CI)	10.85***	(10.74, 10.96)	9.19***	(8.95, 9.42)	10.09***	(9.84, 10.33)	9.21***	(8.88, 9.53)	9.24***	(8.91, 9.56)
Estimates at baseline	**β**	**95% CI**	**β**	**95% CI**	**B**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Oral health										
Excellent (ref)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Good	-0.18*	(-0.34, -0.02)	-0.14	(-0.29, 0.00)	-0.03	(-0.17, 0.11)	-0.01	(-0.15, 0.13)	0.01	(-0.13, 0.14)
Poor	-0.53***	(-0.74, -0.32)	-0.60***	(-0.79, -0.41)	-0.25**	(-0.43, -0.07)	-0.20*	(-0.38, -0.02)	-0.12	(-0.31, 0.06)
Age			-0.12***	(-0.13, -0.11)	-0.11***	(-0.11, -0.10)	-0.11***	(-0.11, -0.10)	-0.11***	(-0.11, -0.10)
Sex			0.73***	(0.59, 0.86)	0.98***	(0.85, 1.11)	1.05***	(0.92, 1.19)	1.09***	(0.96, 1.22)
Marital status										
Married/cohabiting (ref)			0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Single/never married			-0.82***	(-1.12, -0.52)	-0.43**	(-0.71, -0.14)	-0.42**	(-0.71, -0.14)	-0.39**	(-0.68, -0.10)
widowed/divorced			-0.56***	(-0.72, -0.39)	-0.05	(-0.21, 0.11)	-0.04	(-0.20, 0.12)	0.03	(-0.13, 0.19)
Education										
High Education (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Medium Education					-0.76***	(-0.91, -0.61)	-0.73***	(-0.88, -0.58)	-0.72***	(-0.87, -0.57)
No Education					-1.87***	(-2.06, -1.69)	-1.76***	(-1.94, -1.58)	-1.73***	(-1.91, -1.54)
Wealth										
Highest (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
4th Quintile					-0.43***	(-0.62, -0.24)	-0.39***	(-0.57, -0.20)	-0.37***	(-0.56, -0.19)
3rd Quintile					-0.65***	(-0.84, -0.45)	-0.53***	(-0.72, -0.33)	-0.51***	(-0.70, -0.31)
2nd Quintile					-1.07***	(-1.28, -0.87)	-0.92***	(-1.13, -0.71)	-0.88***	(-1.09, -0.67)
Lowest					-1.47***	(-1.70, -1.24)	-1.24***	(-1.47, -1.01)	-1.17***	(-1.40, -0.93)
Smoking										
Non-smoker (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Former smoker							0.02	(-0.12, 0.15)	0.03	(-0.11, 0.17)
Current smoker							-0.20*	(-0.40, -0.00)	-0.17	(-0.37, 0.03)
Alcohol										
Less than daily (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Daily							0.98***	(0.77, 1.19)	0.93***	(0.72, 1.14)
Depressive symptoms										
No (ref)									0	(0.00, 0.00)
Yes									-0.10***	(-0.14, -0.07)

(Cont. Table 6.2)

	Model 1		Model 2		Model 3		Model 4		Model 5	
Estimates of the rate of Change	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Memory change over time	-0.20***	(-0.22, -0.17)	0.11***	(0.05, 0.17)	0.11***	(0.04, 0.18)	0.11*	(0.02, 0.20)	0.11*	(0.02, 0.20)
Oral health										
Good oral health	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.01)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)
Poor oral health	0.02	(-0.03, 0.07)	-0.01	(-0.05, 0.04)	0.01	(-0.05, 0.05)	0.01	(-0.05, 0.05)	0.01	(-0.04, 0.06)
Age			-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)
Sex			0.01	(-0.02, 0.05)	0.02	(-0.02, 0.05)	0.01	(-0.02, 0.05)	0.01	(-0.02, 0.05)
Marital status										
Single/never married			-0.02	(-0.10, 0.05)	-0.02	(-0.10, 0.06)	-0.02	(-0.10, 0.06)	-0.02	(-0.10, 0.06)
widowed/divorced			-0.03	(-0.07, 0.01)	-0.02	(-0.07, 0.02)	-0.02	(-0.07, 0.02)	-0.02	(-0.06, 0.03)
Education										
Medium Education					-0.01	(-0.05, 0.03)	-0.01	(-0.05, 0.03)	-0.01	(-0.05, 0.03)
No Education					-0.02	(-0.07, 0.03)	-0.02	(-0.07, 0.03)	-0.01	(-0.06, 0.04)
Wealth										
4th Quintile					-0.05	(-0.09, 0.00)	-0.05	(-0.10, 0.00)	-0.05	(-0.10, 0.00)
3rd Quintile					-0.06*	(-0.11, -0.01)	-0.07*	(-0.12, -0.02)	-0.07*	(-0.12, -0.01)
2nd Quintile					-0.05	(-0.10, 0.01)	-0.05	(-0.11, 0.00)	-0.05	(-0.10, 0.01)
Lowest Quintile					-0.04	(-0.10, 0.02)	-0.04	(-0.10, 0.02)	-0.03	(-0.10, 0.03)
Smoking										
Former smoker							-0.02	(-0.05, 0.02)	-0.02	(-0.05, 0.02)
Current smoker							-0.04	(-0.10, 0.01)	-0.04	(-0.10, 0.01)
Alcohol										
Daily							0.004	(-0.05, 0.06)	0.002	(-0.05, 0.06)
Depressive symptoms										
Yes									-0.01	(-0.02, 0.00)
Variance										
In the rate of change	0.13		0.10		0.10		0.10		0.10	
In the baseline	7.13		5.23		4.33		4.24		4.21	
Covariance	0.18		-0.02		-0.03		-0.03		-0.03	
Goodness of fit										
Log-Likelihood	-85636.08		-84239.26		-83689.83		-83628.17		-83601.759	
AIC	171292.20		168514.50		167439.7		167332.3		167283.5	
BIC	171376.70		168666.80		167693.4		167653.7		167621.8	
LR test *p*-value			<0.001		<0.001		<0.001		<0.001	

Model 1: Adjusted for self-reported oral health + time and interaction of time with self-reported oral health.
Model 2: Adjusted for model 1 + age, sex, marital status and the interactions of time with age, sex, marital status
Model 3: Adjusted for model 2 + education, wealth and the interactions of time with education and wealth
Model 4: Adjusted for model 3 + smoking, alcohol and the interactions of time with smoking and alcohol
Model 5: Adjusted for model 4 + depressive symptoms and the interaction of time with depressive symptoms
p-value *<0.05, ** <0.01, ***<0.001

6.2.2 Edentulism and the rate of change in memory

In this section, the results of *linear mixed-effects models* of the longitudinal association between edentulism at wave 3 and the rate of memory change from wave 3 to wave 8 are presented (Table 6.3). Overall, edentate participants at wave 3 had a faster rate of decline than dentate participants; however, this association was explained by adjusting for demographic factors. More details were presented in the following paragraphs.

In model 1, the average memory at baseline was 12.99 (95% CI: 12.74, 13.24) controlling for time, edentulism and its interaction with time. The rate of memory change in this model was positive, suggesting an increase over time (β= 0.02, 95% CI: -0.05, 0.08); although, the estimate of memory change was non-significant. Edentate participants had significantly faster memory decline (β= -0.19, 95% CI: -0.25, -0.14). The group-level slope and intercepts variances in this model were 0.13 and 6.66. The covariance in this model was positive (0.15) and the rate of memory change was positive, which means that participants who had higher memory at baseline had steeper slopes, and those who had lower memory at baseline had shallower slopes.

In model 2, the impact of edentulism on the rate of memory change was attenuated considerably by adjusting for demographics (age, sex and marital status in model 2) and became non-significant (β= -0.04, 95% CI: -0.10, 0.01). The impact of age on the rate of memory change was similar to the presented figures presented in the previous section, for each year increase in age, the rate of memory decline (β= -0.02, 95% CI: -0.02, -0.02). This association between age and the rate of memory change was sustained to the fully adjusted model. The group-level slope and intercepts variances in this model got reduced to 0.10 and 5.17.

In model 3, after additionally adjusting for education, wealth and their interactions with time, the association between baseline edentulism and memory at baseline was attenuated substantially yet remained significant (β= -0.34, 95% CI: -0.53, -0.14). The impact of edentulism at wave 3 on memory change got slightly attenuated (β= -0.03, 95% CI: -0.09, 0.02).

In model 4, the association between edentulism and memory at baseline become slightly attenuated; however, it remained significant (β= -0.28; 95% CI: -0.47, -

0.08). The impact of edentulism on the rate of memory change did not get affected by controlling for lifestyle behaviours and was not significant.

Finally, in model 5, the adjustment of depressive symptoms had a very minimal impact on the intercepts and the slopes. Memory at baseline increased (β= 9.53; 95% CI: 9.15, 9.91) and the rate of memory change slightly increase and remained significant (β= 0.13; 95% CI: 0.03, 0.23). The association between edentulism and the rate of memory change still non-significant and did not change in this model (β= -0.03, 95% CI: -0.09, 0.02).

Table 6.3 The results from linear mixed models of edentulism at wave 3 on memory change over 10-years. (n=6,998), β (95% CI)

Outcome: Memory change (wave 3 - wave 8)	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
Memory Mean (95% CI)	12.99***	(12.74, 13.24)	10.16***	(9.85, 10.48)	10.40***	(10.09, 10.72)	9.47***	(9.09, 9.85)	9.53***	(9.15, 9.91)
Estimates at baseline	**β**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Edentulism										
Dentate (ref)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Edentate	-2.01***	(-2.22, -1.81)	-1.00***	(-1.20, -0.80)	-0.34***	(-0.53, -0.14)	-0.28**	(-0.47, -0.08)	-0.29**	(-0.48, -0.09)
Age			-0.11***	(-0.12, -0.10)	-0.10***	(-0.11, -0.10)	-0.10***	(-0.11, -0.09)	-0.10***	(-0.11, -0.10)
Sex			0.77***	(0.63, 0.90)	0.99***	(0.86, 1.12)	1.06***	(0.93, 1.20)	1.10***	(0.97, 1.23)
Marital status										
Married/cohabiting (ref)			0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Single/never married			-0.85***	(-1.15, -0.55)	-0.45**	(-0.74, -0.16)	-0.44**	(-0.73, -0.16)	-0.41**	(-0.69, -0.12)
widowed/divorced			-0.54***	(-0.70, -0.37)	-0.06	(-0.22, 0.11)	-0.05	(-0.21, 0.11)	0.03	(-0.14, 0.19)
Education										
High Education (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Medium Education					-0.76***	(-0.91, -0.61)	-0.73***	(-0.88, -0.58)	-0.72***	(-0.87, -0.57)
No Education					-1.85***	(-2.04, -1.67)	-1.75***	(-1.93, -1.56)	-1.71***	(-1.89, -1.52)
Wealth										
Highest (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
4th Quintile					-0.43***	(-0.61, -0.24)	-0.38***	(-0.57, -0.20)	-0.37***	(-0.56, -0.18)
3rd Quintile					-0.64***	(-0.83, -0.44)	-0.52***	(-0.71, -0.32)	-0.49***	(-0.69, -0.30)
2nd Quintile					-1.05***	(-1.26, -0.84)	-0.90***	(-1.11, -0.70)	-0.86***	(-1.06, -0.65)
Lowest					-1.44***	(-1.67, -1.21)	-1.21***	(-1.45, -0.98)	-1.13***	(-1.36, -0.90)
Smoking										
Non-smoker (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Former smoker							0.02	(-0.12, 0.16)	0.04	(-0.10, 0.18)
Current smoker							-0.19	(-0.39, 0.01)	-0.15	(-0.35, 0.05)
Alcohol										
No alcohol (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Daily							0.97***	(0.76, 1.18)	0.92***	(0.71, 1.13)
Depressive symptoms										
No (ref)									0	(0.00, 0.00)
Yes									-0.11***	(-0.14, -0.07)

(Cont. Table 6.3)

	Model 1		Model 2		Model 3		Model 4		Model 5	
Estimates of the rate of change	**β**	**95% CI**	**B**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Memory change over time	0.02	(-0.05, 0.08)	0.12**	(0.04, 0.20)	0.13**	(0.04, 0.21)	0.12*	(0.02, 0.23)	0.13*	(0.03, 0.23)
Edentulism										
Edentate	-0.19***	(-0.25, -0.14)	-0.04	(-0.10, 0.01)	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)
Age			-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)
Sex			0.01	(-0.02, 0.05)	0.02	(-0.02, 0.05)	0.01	(-0.02, 0.05)	0.01	(-0.02, 0.05)
Marital status										
Single/never married			-0.02	(-0.10, 0.05)	-0.02	(-0.10, 0.06)	-0.02	(-0.10, 0.06)	-0.02	(-0.10, 0.06)
widowed/divorced			-0.03	(-0.07, 0.01)	-0.02	(-0.07, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.03)
Education										
Medium Education					-0.01	(-0.05, 0.03)	-0.01	(-0.05, 0.03)	-0.01	(-0.05, 0.03)
No Education					-0.01	(-0.06, 0.03)	-0.01	(-0.06, 0.04)	-0.01	(-0.06, 0.04)
Wealth										
4th Quintile					-0.04	(-0.09, 0.00)	-0.05	(-0.10, 0.00)	-0.05	(-0.10, 0.00)
3rd Quintile					-0.06*	(-0.11, -0.01)	-0.07*	(-0.12, -0.01)	-0.06*	(-0.12, -0.01)
2nd Quintile					-0.05	(-0.10, 0.01)	-0.05	(-0.10, 0.01)	-0.05	(-0.10, 0.01)
Lowest Quintile					-0.04	(-0.10, 0.02)	-0.04	(-0.10, 0.03)	-0.03	(-0.09, 0.03)
Smoking										
Former smoker							-0.02	(-0.05, 0.02)	-0.02	(-0.05, 0.02)
Current smoker							-0.04	(-0.10, 0.01)	-0.04	(-0.09, 0.02)
Alcohol										
Daily							0.003	(-0.05, 0.06)	0.002	(-0.06, 0.06)
Depressive symptoms										
Yes									-0.01	(-0.02, 0.00)
Variance										
In the rate of change	0.13		0.10		0.10		0.10		0.10	
In the baseline	6.66		5.17		4.33		4.24		4.20	
Covariance	0.15		-0.02		-0.03		-0.03		-0.03	
Goodness of fit										
Log Likelihood	-85385.5		-84197.91		-83685.08		-83624.5		-83595.73	
AIC	170787.1		168427.8		167426.2		167321		167267.5	
BIC	170854.7		168563.1		167662.9		167625.5		167588.8	
LR test *p*-value			<0.001		<0.001		<0.001		<0.001	

Model 1: Adjusted for edentulism + time and interaction of time with edentulism.
Model 2: Adjusted for model 1 + age, sex, marital status and the interactions of time with age, sex, marital status
Model 3: Adjusted for model 2 + education, wealth and the interactions of time with education and wealth
Model 4: Adjusted for model 3 + smoking, alcohol and the interactions of time with smoking and alcohol
Model 5: Adjusted for model 4 + depressive symptoms and the interaction of time with depressive symptoms
p-value *<0.05, ** <0.01, ***<0.001

6.2.3 Oral impacts and the rate of change in memory

In this section, the longitudinal association between oral impacts at wave 3 and the rate of memory change over 10 years is presented (Table 6.4). The results showed that oral impacts at wave 3 were associated with faster memory decline. This significant association was sustained until depressive symptoms were included in model 6, the association marginally became non-significant. More details of each model are presented in this section.

Model 1 included only the exposure variable with its interaction with time. In this model, participants who reported having at least one oral impact remembered fewer words than those who reported no oral impact at baseline (β= -0.37, 95% CI: -0.55, -0.19). They also had a significantly faster memory decline over the next 10 years (β= -0.10, 95% CI: -0.17, -0.04). The average memory at baseline was 10.73 (95% CI: 10.65, 10.80) and the rate of memory change was declining (β= -0.09, 95% CI: -0.16, -0.02). The group-level slope variance was 0.13 and the group-level intercept variance was 7.14.

In model 2, the association between oral impacts and the rate of memory change got attenuated slightly but remained significant (β= -0.08, 95% CI: -0.14, -0.02). Both, the group-level slope and intercept variances, got reduced in this model, 0.10 and 5.26 respectively.

Introducing socioeconomic factors (education and wealth in model 3) considerably attenuated the association of oral impacts with baseline memory (β= -0.21, 95% CI: -0.37, -0.06), and slightly attenuated the association with memory decline (β= -0.07, 95% CI: -0.13, -0.01). Similar to what was observed and reported in the previous section, those who were in the middle wealth group (3rd quintile), had a faster memory decline (β= -0.06, 95% CI: -0.11, -0.01).

Further adjusting for lifestyle behaviours (smoking and alcohol) in model 4 slightly attenuated the association with memory at baseline (β= -0.17, 95% CI: -0.33, -0.02); however, the association with memory decline remained significant and did not change (β= -0.07, 95% CI: -0.13, -0.01). Both, the group-level slope and intercept variances, got reduced in this model, 0.09 and 4.24 respectively.

Finally, including baseline depressive symptoms in the full model (Model 5) contributed to an additional attenuation of the marginally significant association

between baseline oral impacts (wave 3) and the rate of change in memory (β= -0.06, 95% CI: -0.12, 0.00). The average memory at baseline was 9.23 (95% CI: 8.91, 9.54) and the rate of change in memory remained significant in the fully adjusted model (β= -0.17, 95% CI: -0.33, -0.02).

Table 6.4 The results from linear mixed models of oral impacts at wave 3 on memory change over 10-years. (n=6,998), β (95% CI)

Outcome: Memory change (wave 3 - wave 8)	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
Memory Mean (95% CI)	10.73***	(10.65, 10.80)	9.05***	(8.82, 9.27)	10.05***	(9.81, 10.28)	9.18***	(8.86, 9.50)	9.23***	(8.91, 9.54)
Estimates at baseline	**β**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Oral impacts										
No impacts (ref)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
At least one impact	-0.37***	(-0.55, -0.19)	-0.37***	(-0.53, -0.20)	-0.21**	(-0.37, -0.06)	-0.17*	(-0.33, -0.02)	-0.11	(-0.26, 0.05)
Age			-0.12***	(-0.13, -0.11)	-0.11***	(-0.11, -0.10)	-0.10***	(-0.11, -0.10)	-0.11***	(-0.11, -0.10)
Sex			0.75***	(0.61, 0.88)	0.99***	(0.86, 1.12)	1.06***	(0.93, 1.19)	1.09***	(0.96, 1.23)
Marital status										
Married/cohabiting (ref)			0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Single/never married			-0.86***	(-1.16, -0.56)	-0.44**	(-0.73, -0.15)	-0.43**	(-0.72, -0.15)	-0.40**	(-0.68, -0.11)
widowed/divorced			-0.58***	(-0.75, -0.42)	-0.05	(-0.21, 0.11)	-0.04	(-0.21, 0.12)	0.03	(-0.14, 0.19)
Education										
High Education (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Medium Education					-0.76***	(-0.91, -0.61)	-0.73***	(-0.88, -0.58)	-0.72***	(-0.87, -0.57)
No Education					-1.88***	(-2.06, -1.70)	-1.77***	(-1.95, -1.58)	-1.73***	(-1.91, -1.55)
Wealth										
Highest (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
4th Quintile					-0.43***	(-0.62, -0.24)	-0.38***	(-0.57, -0.20)	-0.37***	(-0.56, -0.19)
3rd Quintile					-0.65***	(-0.85, -0.46)	-0.53***	(-0.72, -0.33)	-0.51***	(-0.70, -0.31)
2nd Quintile					-1.08***	(-1.29, -0.88)	-0.93***	(-1.13, -0.72)	-0.89***	(-1.09, -0.68)
Lowest					-1.48***	(-1.71, -1.25)	-1.25***	(-1.48, -1.02)	-1.17***	(-1.40, -0.94)
Smoking										
Non-smoker (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Former smoker							0.01	(-0.12, 0.15)	0.03	(-0.11, 0.17)
Current smoker							-0.21*	(-0.41, -0.01)	-0.17	(-0.37, 0.03)
Alcohol										
Less than daily (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Daily							0.98***	(0.77, 1.19)	0.93***	(0.72, 1.14)
Depressive symptoms										
No (ref)									0	(0.00, 0.00)
Yes									-0.10***	(-0.14, -0.07)

(Cont. Table 6.4)

	Model 1		Model 2		Model 3		Model 4		Model 5	
Estimates of the rate of change	**β**	**95% CI**	**B**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Memory change over time	-0.09*	(-0.16, -0.02)	0.19***	(0.10, 0.27)	0.18***	(0.09, 0.27)	0.17**	(0.06, 0.28)	0.17**	(0.06, 0.28)
Oral impacts										
At least one impact	-0.10**	(-0.17, -0.04)	-0.08**	(-0.14, -0.02)	-0.07*	(-0.13, -0.01)	-0.07*	(-0.13, -0.01)	-0.06	(-0.12, 0.00)
Age			-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)	-0.02***	(-0.02, -0.02)
Sex			0.01	(-0.02, 0.05)	0.02	(-0.02, 0.05)	0.01	(-0.02, 0.05)	0.01	(-0.02, 0.05)
Marital status										
Single/never married			-0.02	(-0.10, 0.05)	-0.02	(-0.10, 0.06)	-0.02	(-0.10, 0.06)	-0.02	(-0.10, 0.06)
widowed/divorced			-0.03	(-0.07, 0.01)	-0.02	(-0.07, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.03)
Education										
Medium Education					-0.01	(-0.05, 0.03)	-0.01	(-0.05, 0.03)	-0.01	(-0.05, 0.03)
No Education					-0.02	(-0.07, 0.03)	-0.02	(-0.07, 0.03)	-0.01	(-0.06, 0.03)
Wealth										
4th Quintile					-0.04	(-0.09, 0.00)	-0.05	(-0.10, 0.00)	-0.05	(-0.10, 0.00)
3rd Quintile					-0.06*	(-0.11, -0.01)	-0.07*	(-0.12, -0.02)	-0.07*	(-0.12, -0.01)
2nd Quintile					-0.05	(-0.10, 0.01)	-0.05	(-0.10, 0.01)	-0.05	(-0.10, 0.01)
Lowest Quintile					-0.04	(-0.10, 0.02)	-0.04	(-0.10, 0.03)	-0.03	(-0.09, 0.03)
Smoking										
Former smoker							-0.02	(-0.05, 0.02)	-0.02	(-0.05, 0.02)
Current smoker							-0.04	(-0.09, 0.02)	-0.04	(-0.09, 0.02)
Alcohol										
Daily							0.001	(-0.06, 0.06)	0.0003	(-0.06, 0.06)
Depressive symptoms										
Yes									-0.01	(-0.01, 0.00)
Variance										
In the rate of change	0.13		0.10		0.10		0.09		0.09	
In the baseline	7.14		5.26		4.33		4.24		4.21	
Covariance	0.18		-0.02		-0.03		-0.03		-0.03	
Goodness of fit										
Log Likelihood	-85631.5		-84245.8		-83684.7		-83623.76		-83599	
AIC	171279		168524		167425.3		167319.5		167274	
BIC	171347		168659		167662.1		167624		167595.4	
LR test P-value			<0.001		<0.001		<0.001		<0.001	

Model 1: Adjusted for oral impacts + time and interaction of time with oral impacts.
Model 2: Adjusted for model 1 + age, sex, marital status and the interactions of time with age, sex, marital status
Model 3: Adjusted for model 2 + education, wealth and the interactions of time with education and wealth
Model 4: Adjusted for model 3 + smoking, alcohol and the interactions of time with smoking and alcohol
Model 5: Adjusted for model 4 + depressive symptoms and the interaction of time with depressive symptoms
p-value *<0.05, ** <0.01, ***<0.001

6.3 Oral health and the rate of change in executive function

In this section, the results of the *Linear Mixed Models* for the associations between oral health at wave 3 and the rate of executive function change from wave 3 to wave 8 are presented (Table 6.5).

6.3.1 Self-reported oral health and the rate of change in executive function

In model 1, the average executive function score at baseline was 21.21 (95% CI: 21.00, 21.43) adjusting for time, self-reported oral health and its interaction with time. The rate of executive function change over time was -0.16 (95% CI: -0.21, -0.11). Participants who reported good or poor oral health significantly named fewer animals than those who reported excellent oral health at baseline; however, the impact of self-reported oral health on the rate of executive function change was not significant. For example, participants who reported good oral health at wave 3 had a faster executive function decline (β= -0.01, 95% CI: -0.08, 0.07); although it was not significant. Participants who reported good or poor oral health significantly had a lower executive function at baseline. The group-level slope variance was 0.55 and the group-level intercept variance was 27.59.

In model 2, further control for demographic factors (age, sex and marital status) strengthened the association between poor oral health and baseline executive function (β= -1.18, 95% CI: 1.56, -0.79) and attenuated the association between poor oral health and executive function rate of change (β= 0.04, 95% CI: -0.05, 0.14); although the impact of poor oral health on the rate of change was not significant. Age was significantly associated with the rate of executive change in this model (β= -0.03, 95% CI: -0.03, -0.02). Furthermore, the rate of change in executive function increased after adjusting for demographics (β= 0.24, 95% CI: 0.12, 0.36). In model 2, both the group-level slope and intercept variances were reduced substantially to 23.41 and 0.49.

In model 3, further control for education and wealth considerably attenuated the association of self-reported oral health with executive function at baseline. The impact of self-reported oral health on the rate of change remained non-significant and did not change in this model. The average executive function increased in this model to 22.95 (95% CI: 22.44, 23.46); on the other hand, the rate of executive function change decreased (β= 0.24, 95% CI: 0.12, 0.36). Participants in the 2nd

quintile of wealth significantly had faster executive function decline (β= -0.18, 95% CI: -0.29, -0.07). The group-level intercept variance considerably reduced in this model to 20.65, while the group-level slope variance reduced slightly to 0.48.

In model 4, controlling the lifestyle behaviours and their interactions with time reduced the average executive function at baseline (β= 21.34, 95% CI: 20.66, 22.02) and increased the rate of executive function change (β= 0.28, 95% CI: 0.10, 0.46). Participants who reported being current or former smokers had a faster decline in executive function; although the association was not significant.

Finally, in the fully adjusted model, depressive symptoms and their interactions with time were introduced. In this model, both the average executive function at baseline (β= 21.40, 95% CI: 20.72, 22.08) and the rate of executive function change (β= 0.29, 95% CI: 0.11, 0.47) slightly increased. In the fully adjusted model, the association between self-reported oral health and the rate of executive function change remained not significant. Participants who reported higher depressive symptoms at wave 3 had faster executive function decline (β= -0.02, 95% CI: -0.04, -0.001).

Table 6.5 The results from linear mixed models of self- reported oral health at wave 3 on 10-year executive function change (n=6,998), β (95% CI)

Outcome: Executive function change (wave 3 - wave 8)	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
Executive function Mean (95% CI)	21.21***	(21.00, 21.43)	21.25***	(20.76, 21.73)	22.95***	(22.44, 23.46)	21.34***	(20.66, 22.02)	21.40***	(20.72, 22.08)
Estimates at baseline	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Oral health										
Excellent (ref)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Good	-0.49**	(-0.81, -0.17)	-0.43**	(-0.73, -0.13)	-0.24	(-0.53, 0.05)	-0.21	(-0.49, 0.08)	-0.17	(-0.46, 0.11)
Poor	-1.05***	(-1.46, -0.64)	-1.18***	(-1.56, -0.79)	-0.60**	(-0.98, -0.23)	-0.50**	(-0.88, -0.13)	-0.37	(-0.74, 0.01)
Age			-0.18***	(-0.19, -0.16)	-0.15***	(-0.16, -0.13)	-0.14***	(-0.16, -0.13)	-0.15***	(-0.16, -0.13)
Sex			-0.44**	(-0.72, -0.16)	0.04	(-0.23, 0.31)	0.17	(-0.11, 0.45)	0.24	(-0.04, 0.52)
Marital status										
Married/cohabiting (ref)			0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Single/never married			-1.51***	(-2.12, -0.89)	-0.92**	(-1.52, -0.32)	-0.91**	(-1.50, -0.31)	-0.85**	(-1.44, -0.25)
widowed/divorced			-1.04***	(-1.37, -0.70)	-0.24	(-0.58, 0.09)	-0.23	(-0.56, 0.11)	-0.10	(-0.44, 0.25)
Education										
High Education (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Medium Education					-1.65***	(-1.97, -1.34)	-1.61***	(-1.93, -1.30)	-1.59***	(-1.91, -1.27)
No Education					-3.52***	(-3.89, -3.14)	-3.32***	(-3.70, -2.94)	-3.26***	(-3.64, -2.88)
Wealth										
Highest (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
4th Quintile					-0.90***	(-1.30, -0.51)	-0.83***	(-1.23, -0.44)	-0.81***	(-1.20, -0.42)
3rd Quintile					-1.23***	(-1.64, -0.82)	-1.03***	(-1.44, -0.62)	-0.99***	(-1.40, -0.58)
2nd Quintile					-1.63***	(-2.06, -1.20)	-1.37***	(-1.80, -0.94)	-1.29***	(-1.73, -0.86)
Lowest					-2.29***	(-2.76, -1.82)	-1.88***	(-2.36, -1.39)	-1.74***	(-2.22, -1.25)
Smoking										
Non-smoker (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Former smoker							0.04	(-0.25, 0.33)	0.06	(-0.22, 0.35)
Current smoker							-0.43*	(-0.85, -0.01)	-0.36	(-0.78, 0.06)
Alcohol										
Less than daily (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Daily							1.75***	(1.31, 2.19)	1.66***	(1.22, 2.10)
Depressive symptoms										
No (ref)									0	(0.00, 0.00)
Yes									-0.19***	(-0.26, -0.12)

(Cont. Table 6.5)

	Model 1		Model 2		Model 3		Model 4		Model 5	
Estimates of ate of change	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Executive function change over time	-0.16***	(-0.21, -0.11)	0.24***	(0.12, 0.36)	0.20**	(0.07, 0.33)	0.28**	(0.10, 0.46)	0.29**	(0.11, 0.47)
Oral health										
Good oral health	-0.01	(-0.08, 0.07)	-0.01	(-0.09, 0.06)	-0.01	(-0.08, 0.07)	-0.01	(-0.08, 0.07)	-0.006	(-0.08, 0.07)
Poor oral health	0.08	(-0.02, 0.18)	0.04	(-0.05, 0.14)	0.06	(-0.04, 0.16)	0.06	(-0.04, 0.16)	0.07	(-0.03, 0.17)
Age			-0.03***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)
Sex			0.03	(-0.04, 0.10)	0.03	(-0.04, 0.10)	0.02	(-0.05, 0.09)	0.03	(-0.04, 0.10)
Marital status										
Single/never married			-0.06	(-0.21, 0.10)	-0.04	(-0.20, 0.12)	-0.04	(-0.19, 0.12)	-0.03	(-019, 0.13)
widowed/divorced			-0.03	(-0.12, 0.05)	0.01	(-0.09, 0.09)	0.01	(-0.09, 0.09)	0.01	(-0.08, 0.10)
Education										
Medium Education					0.03	(-0.05, 0.11)	0.03	(-0.05, 0.11)	0.03	(-0.05, 0.11)
No Education					0.02	(-0.08, 0.12)	0.01	(-0.09, 0.11)	0.02	(-0.08, 0.12)
Wealth										
4th Quintile					-0.01	(-0.11, 0.09)	-0.02	(-0.12, 0.08)	-0.02	(-0.11, 0.08)
3rd Quintile					-0.04	(-0.14, 0.06)	-0.05	(-0.16, 0.05)	-0.05	(-0.15, 0.06)
2nd Quintile					-0.18**	(-0.29, -0.07)	-0.19***	(-0.30, -0.08)	-0.18**	(-0.29, -0.07)
Lowest Quintile					-0.08	(-0.20, 0.04)	-0.09	(-0.22, 0.04)	-0.07	(-0.20, 0.05)
Smoking										
Former smoker							-0.02	(-0.09, 0.05)	-0.02	(-0.09, 0.06)
Current smoker							-0.06	(-0.17, 0.06)	-0.05	(-0.16, 0.06)
Alcohol										
Daily							-0.08	(-0.20, 0.03)	-0.09	(-0.21, 0.03)
Depressive symptoms										
Yes									-0.02*	(-0.04, -0.00)
Variance										
In the rate of change	0.55		0.49		0.48		0.48		0.48	
In baseline	27.59		23.41		20.65		20.36		20.25	
Covariance	-0.27		-0.60		-0.62		-0.60		-0.62	
Goodness of fit										
Log Likelihood	-91158.02		-90418.27		-90022.88		-89984.56		-89959.904	
AIC	182336.00		180872.50		180105.8		180045.1		179999.8	
BIC	182418.80		181021.60		180354.1		180359.7		180330.9	
LR test P-value			<0.001		<0.001		<0.001		<0.001	

Model 1: Adjusted for self-reported oral health + time and interaction of time with self-reported oral health.
Model 2: Adjusted for model 1 + age, sex, marital status and the interactions of time with age, sex, marital status
Model 3: Adjusted for model 2 + education, wealth and the interactions of time with education and wealth
Model 4: Adjusted for model 3 + smoking, alcohol and the interactions of time with smoking and alcohol
Model 5: Adjusted for model 4 + depressive symptoms and the interaction of time with depressive symptoms
p-value *<0.05, ** <0.01, ***<0.001

6.3.2 Edentulism and the rate of change in executive function

This section will present the findings from the *linear mixed-effects models* of the longitudinal association between edentulism at wave 3 and the rate of executive function change from wave 3 to wave 8 (Table 6.5). The results showed a strong association in the unadjusted model; however, controlling for demographic factors in model 2 substantially attenuated that association. More details are presented in this section below.

In model 1, only the baseline edentulism and its interaction with time were included in the model. Participants who were edentate at baseline named significantly fewer animals (β= -3.42, 95 % CI: -3.83, -3.01); and also, they had faster executive function decline (β= -0.31 95 % CI: -0.42, -0.21) compared to dentate participants. The average baseline executive function in this model was 24.75 (95% CI: 24.27, 25.24) and the rate of executive function change every two years was 0.20 (95% CI: 0.07, 0.32). The group-level slope variance was 0.54 and the variance of the intercept was 26.24.

In model 2, adjusting for demographic factors and their interactions with time considerably attenuated the impact of edentulism on executive function at baseline (β= -1.85, 95% CI: -2.25, -1.44), and on the rate of executive function change (β= -0.12, 95% CI: -0.23, -0.01); however, both remained significant. In this model also, the baseline average executive function reduced (β= 22.97, 95 % CI: 22.32, 23.62); while the rate of change of executive function increased (β= 0.32, 95 % CI: 0.16, 0.49). The variances of the group-level slope and intercept reduced, 0.49 and 23.21 respectively.

In model 3, further adjusting for socioeconomic factors and their interactions with time continued attenuating the association between edentulism and executive function at baseline (β= -0.75, 95% CI: -1.16, -0.35). Additionally, the impact of edentulism on the rate of executive function changed slightly and became non-significant (β= -0.1, 95% CI; -0.21, 0.01). Similar to what was observed in the previous section, participants among the 2nd quintile of wealth significantly had faster executive function decline (β= -0.16, 95% CI: -0.27, -0.05). The results of this model also showed an increase in the baseline executive function (β= 23.58, 95 % CI: 22.93, 24.24) and a decrease in the rate of change of executive function (β= 0.29, 95 % CI: 0.12, 0.46).

In model 4, adjusting for lifestyle behaviours (smoking and alcohol) and their interaction terms with time attenuated the association between edentulism and the baseline executive function (β= -0.64, 95% CI: -1.05, -0.24). The association between edentulism and the rate of executive function change did not change and remain non-significant (β= -0.10, 95% CI: -0.21, 0.01). The group-level slope variance did not change in this model, and a minor decrease was observed in the group-level intercept.

Finally, the fully adjusted model included all covariates and their interactions with time. The results from adjusting for depressive symptoms and its interaction with time in this model showed a slightly stronger association of edentulism with baseline executive function (β= -0.66, 95% CI: -1.07, -0.26); but did not have any considerable impact on the rate of executive function change. Both the average baseline of executive function and its rate of change slightly increased in this model. The variances of the group-level slope and intercept did not change in this model.

Table 6.6 The results from linear mixed models of edentulism at wave 3 on 10-year executive function change (n=6,998), β (95% CI)

Outcome: Executive function change (wave 3 - wave 8)	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
Executive function Mean (95% CI)	24.75***	(24.27, 25.24)	22.97***	(22.32, 23.62)	23.58***	(22.93, 24.24)	21.88***	(21.08, 22.67)	22.00***	(21.20, 22.79)
Estimates at baseline	**β**	**95% CI**	**B**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Edentulism										
Dentate (ref)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Edentate	-3.42***	(-3.83, -3.01)	-1.85***	(-2.25, -1.44)	-0.75***	(-1.16, -0.35)	-0.64**	(-1.05, -0.24)	-0.66**	(-1.07, -0.26)
Age			-0.15***	(-0.17, -0.14)	-0.14***	(-0.15, -0.12)	-0.14***	(-0.15, -0.12)	-0.14***	(-0.15, -0.12)
Sex			-0.36*	(-0.64, -0.08)	0.07	(-0.20, 0.34)	0.2	(-0.08, 0.47)	0.26	(-0.01, 0.54)
Marital status										
Married/cohabiting (ref)			0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Single/never married			-1.57***	(-2.18, -0.95)	-0.97**	(-1.57, -0.37)	-0.95**	(-1.55, -0.36)	-0.88**	(-1.48, -0.29)
widowed/divorced			-1.01***	(-1.34, -0.67)	-0.27	(-0.60, 0.07)	-0.24	(-0.58, 0.09)	-0.10	(-0.44, 0.24)
Education										
High Education (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Medium Education					-1.66***	(-1.97, -1.34)	-1.61***	(-1.93, -1.30)	-1.59***	(-1.90, -1.27)
No Education					-3.48***	(-3.85, -3.10)	-3.29***	(-3.67, -2.91)	-3.21***	(-3.59, -2.83)
Wealth										
Highest (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
4th Quintile					-0.89***	(-1.28, -0.50)	-0.82***	(-1.22, -0.43)	-0.80***	(-1.19, -0.41)
3rd Quintile					-1.21***	(-1.61, -0.80)	-1.01***	(-1.42, -0.60)	-0.97***	(-1.37, -0.56)
2nd Quintile					-1.57***	(-2.00, -1.14)	-1.32***	(-1.76, -0.89)	-1.23***	(-1.67, -0.80)
Lowest					-2.21***	(-2.69, -1.74)	-1.82***	(-2.30, -1.33)	-1.66***	(-2.14, -1.17)
Smoking										
Non-smoker (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Former smoker							0.05	(-0.24, 0.34)	0.09	(-0.20, 0.37)
Current smoker							-0.40	(-0.82, 0.01)	-0.32	(-0.74, 0.10)
Alcohol										
No alcohol (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Daily							1.74***	(1.30, 2.18)	1.63***	(1.19, 2.07)
Depressive symptoms										
No (ref)										
Yes									-0.20***	(-0.27, -0.13)

(Cont. Table 6.6)

	Model 1		Model 2		Model 3		Model 4		Model 5	
Estimates of the rate of change	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Executive function change over time	0.20**	(0.07, 0.32)	0.32***	(0.16, 0.49)	0.29***	(0.12, 0.46)	0.38***	(0.17, 0.59)	0.39***	(0.18, 0.60)
Edentulism										
Edentate	-0.31***	(-0.42, -0.21)	-0.12*	(-0.23, -0.01)	-0.10	(-0.21, 0.01)	-0.10	(-0.21, 0.01)	-0.10	(-0.21, 0.01)
Age			-0.02***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)
Sex			0.04	(-0.03, 0.10)	0.03	(-0.04, 0.10)	0.02	(-0.05, 0.09)	0.03	(-0.04, 0.10)
Marital status										
Single/never married			-0.05	(-0.21, 0.11)	-0.03	(-0.19, 0.13)	-0.03	(-0.19, 0.13)	-0.03	(-0.19, 0.13)
widowed/divorced			-0.02	(-0.11, 0.06)	0.01	(-0.09, 0.09)	0.01	(-0.09, 0.09)	0.01	(-0.08, 0.10)
Education										
Medium Education					0.03	(-0.05, 0.11)	0.03	(-0.05, 0.11)	0.03	(-0.05, 0.11)
No Education					0.03	(-0.07, 0.13)	0.02	(-0.08, 0.12)	0.02	(-0.08, 0.12)
Wealth										
4th Quintile					-0.01	(-0.11, 0.09)	-0.01	(-0.11, 0.09)	-0.01	(-0.11, 0.09)
3rd Quintile					-0.03	(-0.14, 0.07)	-0.05	(-0.15, 0.06)	-0.04	(-0.15, 0.06)
2nd Quintile					-0.16**	(-0.27, -0.05)	-0.18**	(-0.29, -0.06)	-0.17**	(-0.28, -0.05)
Lowest Quintile					-0.06	(-0.18, 0.07)	-0.07	(-0.20, 0.06)	-0.06	(-0.18, 0.07)
Smoking										
Former smoker							-0.01	(-0.09, 0.06)	-0.01	(-0.09, 0.06)
Current smoker							-0.04	(-0.15, 0.07)	-0.04	(-0.15, 0.07)
Alcohol										
Daily							-0.09	(-0.21, 0.03)	-0.10	(-0.22, 0.02)
Depressive symptoms										
Yes									-0.02	(-0.04, 0.00)
Variance										
In rate of change	0.54		0.49		0.48		0.48		0.48	
In the baseline	26.24		23.21		20.63		20.35		20.35	
Covariance	-0.34		-0.61		-0.62		-0.61		-0.61	
Goodness of fit										
Log Likelihood	-90961		-90379		-90015.18		-89978		-89951.29	
AIC	181939		180791		180086		180028		179978.6	
BIC	182005		180923		180318		180326		180293.2	
LR test P-value			<0.001		<0.001		<0.001		<0.001	

Model 1: Adjusted for edentulism + time and interaction of time with edentulism.
Model 2: Adjusted for model 1 + age, sex, marital status and the interactions of time with age, sex, marital status
Model 3: Adjusted for model 2 + education, wealth and the interactions of time with education and wealth
Model 4: Adjusted for model 3 + smoking, alcohol and the interactions of time with smoking and alcohol
Model 5: Adjusted for model 4 + depressive symptoms and the interaction of time with depressive symptoms
p-value *<0.05, ** <0.01, ***<0.001

6.3.3 Oral impacts and the rate of change in executive function

In this set of analyses, the association between baseline oral impacts and the rate of executive function change was investigated. The association was robust in the unadjusted model and further adjusting for the demographics and socioeconomic factors considerably attenuated that association. More details about this matter in the following paragraphs.

In model 1, participants who reported at least one oral impact at baseline named fewer animals (β= -0.86, 95 % CI: -1.21, -0.51) than those who reported no oral impacts (Table 6.7). The association between oral impacts and the rate of executive change over time was small and not-significant (β= -0.06, 95 % CI: -0.18, 0.07). The group-level slope and intercept variances were 0.55 and 27.59; which was very similar to what was observed in Table 5.5 for the self-reported oral health.

In model 2, adjusting for age, sex, marital status and their interactions with time slightly attenuated the association between oral impacts and executive function at baseline (β= -0.80, 95% CI: -1.13, -0.47). Likewise, the association with rate of executive function change was substantially attenuated (β= -0.03, 95 % CI: -0.16, 0.09).

In model 3, further adjusting for education and wealth attenuated the association between oral impacts and executive function at baseline (β= -0.55; 95% CI: -0.86, -0.23). The oral impact on the rate of change in executive function got attenuated by adjusting for socioeconomic factors and their interactions with time (β= -0.01; 95% CI: -0.14, 0.11).

In model 4, further adjusting for lifestyle behaviours attenuated the association between oral impacts and executive function at baseline (β= -0.47, 95% CI: -0.79, -0.15). However, it had no considerable effect on the rate of executive function change.

Finally, in model 5, adjusting for depressive symptoms and its interaction with time attenuated the association between oral impacts and the baseline executive function but did not have any considerable impact on the rate of executive function change.

Table 6.7 The results from linear mixed models of oral impacts at wave 3 on executive function change over 10-years (n=6,998), β (95% CI)

Outcome: Executive function change (wave 3 - wave 8)	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
Executive function Mean (95% CI)	20.93***	(20.78, 21.08)	20.92***	(20.46, 21.38)	22.79***	(22.30, 23.29)	21.21***	(20.55, 21.87)	21.29***	(20.63, 21.95)
Estimates at baseline	**β**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Oral impacts										
No oral impacts (ref)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
At least one impact	-0.86***	(-1.21, -0.51)	-0.80***	(-1.13, -0.47)	-0.55***	(-0.86, -0.23)	-0.47**	(-0.79, -0.15)	-0.34*	(-0.66, -0.02)
Age			-0.17***	(-0.19, -0.16)	-0.14***	(-0.16, -0.13)	-0.14***	(-0.16, -0.13)	-0.14***	(-0.16, -0.13)
Sex			-0.40**	(-0.68, -0.12)	0.07	(-0.21, 0.34)	0.19	(-0.09, 0.47)	0.25	(-0.02, 0.53)
Marital status										
Married/cohabiting (ref)			0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Single/never married			-1.58***	(-2.20, -0.97)	-0.95**	(-1.55, -0.35)	-0.93**	(-1.53, -0.33)	-0.86**	(-1.46, -0.27)
widowed/divorced			-1.08***	(-1.42, -0.75)	-0.25	(-0.59, 0.09)	-0.23	(-0.57, 0.11)	-0.10	(-0.44, 0.24)
Education										
High Education (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
Medium Education					-1.66***	(-1.98, -1.34)	-1.61***	(-1.93, -1.30)	-1.59***	(-1.91, -1.28)
No Education					-3.54***	(-3.91, -3.16)	-3.34***	(-3.72, -2.96)	-3.27***	(-3.65, -2.89)
Wealth										
Highest (ref)					0	(0.00, 0.00)	0	(0.00, 0.00)	0	(0.00, 0.00)
4th Quintile					-0.89***	(-1.29, -0.50)	-0.82***	(-1.22, -0.43)	-0.81***	(-1.20, -0.41)
3rd Quintile					-1.24***	(-1.65, -0.83)	-1.04***	(-1.45, -0.63)	-1.00***	(-1.41, -0.59)
2nd Quintile					-1.64***	(-2.07, -1.22)	-1.38***	(-1.81, -0.95)	-1.30***	(-1.73, -0.87)
Lowest					-2.31***	(-2.78, -1.84)	-1.89***	(-2.37, -1.41)	-1.75***	(-2.23, -1.27)
Smoking										
Non-smoker (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Former smoker							0.03	(-0.25, 0.32)	0.06	(-0.23, 0.35)
Current smoker							-0.43*	(-0.85, -0.01)	-0.37	(-0.78, 0.05)
Alcohol										
No alcohol (ref)							0	(0.00, 0.00)	0	(0.00, 0.00)
Daily							1.75***	(1.31, 2.19)	1.66***	(1.22, 2.10)
Depressive symptoms										
No (ref)									0	(0.00, 0.00)
Yes									-0.19***	(-0.26, -0.11)

(Cont. Table 6.7)

	Model 1		Model 2		Model 3		Model 4		Model 5	
Estimates of the rate of change	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Executive function change over time	-0.09	(-0.23, 0.05)	0.27**	(0.10, 0.45)	0.22*	(0.04, 0.40)	0.30**	(0.08, 0.52)	0.29**	(0.07, 0.51)
Oral impacts										
At least one impact	-0.06	(-0.18, 0.07)	-0.03	(-0.16, 0.09)	-0.01	(-0.14, 0.11)	-0.01	(-0.13, 0.11)	0.01	(-0.12, 0.13)
Age			-0.03***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)	-0.03***	(-0.03, -0.02)
Sex			0.03	(-0.04, 0.10)	0.03	(-0.04, 0.10)	0.02	(-0.05, 0.09)	0.03	(-0.04, 0.10)
Marital status										
Single/never married			-0.05	(-0.21, 0.11)	-0.03	(-0.19, 0.13)	-0.03	(-0.19, 0.13)	-0.03	(-0.19, 0.13)
widowed/divorced			-0.03	(-0.11, 0.06)	0.01	(-0.09, 0.09)	0.01	(-0.09, 0.09)	0.01	(-0.08, 0.10)
Education										
Medium Education					0.03	(-0.05, 0.11)	0.03	(-0.05, 0.11)	0.03	(-0.05, 0.11)
No Education					0.02	(-0.08, 0.12)	0.01	(-0.09, 0.11)	0.02	(-0.08, 0.12)
Wealth										
4th Quintile					-0.01	(-0.11, 0.09)	-0.02	(-0.11, 0.08)	-0.02	(-0.11, 0.08)
3rd Quintile					-0.04	(-0.14, 0.06)	-0.05	(-0.16, 0.05)	-0.05	(-0.15, 0.06)
2nd Quintile					-0.17**	(-0.28, -0.06)	-0.18**	(-0.29, -0.07)	-0.18**	(-0.29, -0.07)
Lowest Quintile					-0.07	(-0.20, 0.05)	-0.08	(-0.21, 0.04)	-0.07	(-0.20, 0.06)
Smoking										
Former smoker							-0.02	(-0.09, 0.06)	-0.02	(-0.09, 0.06)
Current smoker							-0.05	(-0.16, 0.06)	-0.05	(-0.16, 0.06)
Alcohol										
Daily							-0.09	(-0.21, 0.03)	-0.09	(-0.21, 0.03)
Depressive symptoms										
Yes									-0.02	(-0.04, 0.00)
Variance										
In the rate of change	0.55		0.49		0.48		0.48		0.48	
In the baseline	27.59		23.47		20.64		20.35		20.25	
Covariance	-0.28		-0.61		-0.62		-0.61		-0.62	
Goodness of fit										
Log Likelihood	-91156		-90424.11		-90021.5		-89983.44		-89960.1	
AIC	182328		180880.2		180099		180038.9		179996.2	
BIC	182394		181012.7		180330.8		180336.9		180310.8	
LR test P-value			<0.001		<0.001		<0.001		<0.001	

Model 1: Adjusted for oral impacts + time and interaction of time with oral impacts
Model 2: Adjusted for model 1 + age, sex, marital status and the interactions of time with age, sex, marital status
Model 3: Adjusted for model 2 + education, wealth and the interactions of time with education and wealth
Model 4: Adjusted for model 3 + smoking, alcohol and the interactions of time with smoking and alcohol
Model 5: Adjusted for model 4 + depressive symptoms and the interaction of time with depressive symptoms
p-value *<0.05, ** <0.01, ***<0.001

Summary

Overall, the results of the *linear mixed-effects models* for the associations between oral health at wave 3 and the rate of change in cognitive function showed that participants with adverse oral health status, i.e. those who were edentate or who reported some oral impacts had a faster rate of decline in cognitive function. However, the associations were substantially attenuated and explained by adjusting for demographic factors (age, sex and marital status) and socioeconomic factors (education and wealth) and their interactions with time. For participants who reported poor oral health, they had worse cognitive function at baseline than those who reported excellent oral health, but the association with the rate of change was non-significant.

The findings showed a small and non-significant association between the impact of self-reported oral health and the rate of cognitive function change over time was across all models of covariates adjustment. Nevertheless, oral impacts almost predicted memory change; the estimate was so close to being statistically significant in the fully adjusted model after adjusting for depressive symptoms and its interaction with time. The same association of oral impacts with executive function change was weaker and got attenuated by both demographic and socioeconomic factors.

On the other hand, the association between edentulism and memory change was very robust before it was attenuated and explained by controlling for the demographic factors. The association between edentulism and change in executive function was also attenuated substantially by controlling for demographic factors and slightly by controlling for the socioeconomic factors.

THE LONGITUDINAL ASSOCIATION BETWEEN ORAL HEALTH AT WAVE 3 AND COGNITIVE IMPAIRMENT AT WAVE 8

7 THE LONGITUDINAL ASSOCIATION BETWEEN ORAL HEALTH AT WAVE 3 AND COGNITIVE IMPAIRMENT AT WAVE 8

The previous chapters focused on the association between oral health and cognitive function outcomes. These analyses showed a significant association between oral health and prospective cognitive function and cognitive decline. Chapter 4 presented the cross-sectional association between oral health and cognitive function at wave 3. Chapter 5 presented the time-lag and autoregressive linear regression models of the longitudinal association between oral health at wave 3 and cognitive function at wave 8. Chapter 6 presented the results of the *linear mixed-effects models* assessing the longitudinal association between oral health at wave 3 and the rate of change in cognitive function from wave 3 to wave 8.

Since those with lower cognitive function and faster cognitive decline are at higher risk of developing cognitive impairment, this chapter will investigate the longitudinal association between oral health at wave 3 and cognitive impairment at wave 8. The hypothesis tested in this chapter was if poorer oral health at baseline (wave 3) is associated with subsequent cognitive impairment 10-years later (wave 8) (Figure 7.1). The cut-off point used to ascertain cognitive impairment was 1.5 standard deviation below the mean of The Modified Telephone Interview for Cognitive Status (mTICS) (Zietemann et al., 2017). The mean (SD) of mTICS was 24.10 (4.62), and the cut-off point was 17; therefore, participants who scored 0-17 were categorised as cognitively impaired and 18-35 as cognitively normal.

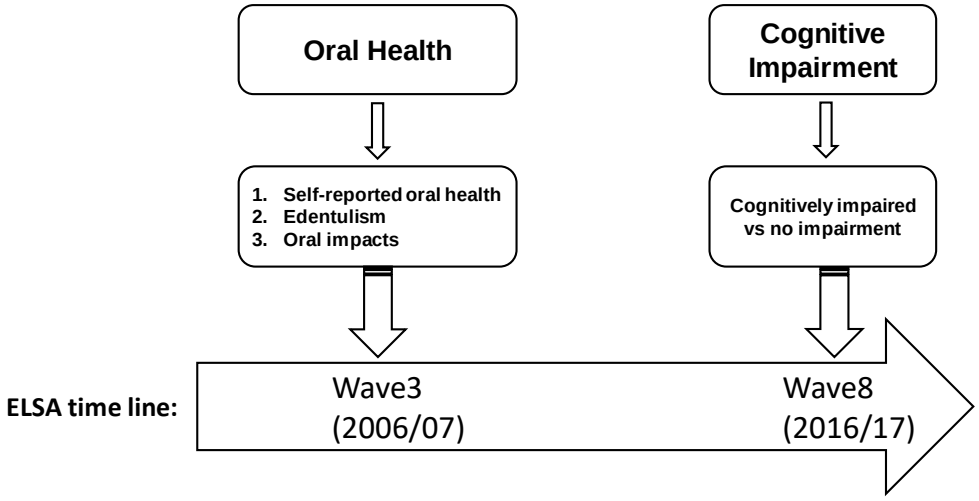

Figure 7.1 The analytical framework of the association between the exposure and outcome variables.

To keep the analysis of this chapter consistent with previous chapters, the sample used was similar to the sample used in chapter 5 (*the longitudinal association between oral health at wave 3 and cognitive functioning at wave 8*). As shown in Table 7.1, the overall prevalence of cognitive impairment at the analytical sample was 332 (8.6%). There was no significant difference between groups of self-reported oral health regarding the prevalence of cognitive impairment (*p*-value= 0.73). Edentate participants had a higher prevalence of cognitive impairment (23.7%) compared to dentate (7.1%), and the difference was statically significant (*p*-value <0.001). For oral impacts, participants who reported oral impacts also had a higher prevalence of cognitive impairment (13.6%) compared to those who reported none (8.2%) (*p*-value= 0.002).

Table 7.1 Oral health characteristics of the sample (N=3,856) at baseline (wave 3) by cognitive impairment at wave 8

	Total	**Cognitive Impairment** (mTICS score ≤ 17)		**[a]P-value**
		n	**(%)**	
Self-reported oral health				
Excellent	1,745	149	(8.5)	
Good	1,482	133	(9.0)	
Poor	629	50	(7.6)	0.730
Edentulism				
Dentate	3,501	248	(7.1)	
Edentate	355	84	(23.7)	<0.001
Oral impacts				
No impact	3,570	293	(8.2)	
At least one impact	286	39	(13.6)	0.002
Overall	**3,856**	332	(8.6)	

[a] **P -values** were calculated using chi-square test

7.1 Oral health and cognitive impairment

This section will primarily present the results of the time-lag logistic regression models between oral health and cognitive impairment. Section 7.1.1 presents the results of the association of self-reported oral health with cognitive impairment, section 7.1.2 for the association of edentulism with cognitive impairment and section 7.1.3 presents the results of the association of oral impacts with cognitive impairment.

The results showed an overall strong association between oral health measures at wave 3 and subsequent cognitive impairment at wave 8 (Table 7.2). The only exception is for the self-reported oral health; the results were statistically not significant. For each section, the results will be shown for the overall sample, then the results of dentate and dentate samples will be presented separately (Table 7.3).

7.1.1 Self-reported oral health and cognitive impairment

As previously mentioned, the association between self-reported oral health at wave 3 and the subsequent cognitive impairment at wave 8 was weak and non-significant across all adjusted models (Table 7.2). In the unadjusted model, participants who reported good oral health at wave 3 were 1.06 (95% CI: 0.66, 1.29) times more likely to have cognitive impairment, while those who reported poor oral health had an odds ratio of 0.93 (95% CI: 0.83, 1.35); however, both associations were non-significant indicating no association between self-reported oral health at wave 3 and cognitive impairment at wave 8.

Controlling for demographic factors (age, sex and marital status in Model 2) strengthened the Odds Ratio (OR) of the associations between those who reported good (OR= 1.15, 95% CI: 0.89, 1.49) or poor oral health (OR= 1.11, 95% CI: 0.78, 1.57) and cognitive impairment.

On the other hand, socioeconomic factors (education and wealth in Model 3) attenuated the association between participants who reported good (OR= 1.06, 95% CI: 0.81, 1.39) or poor oral health (OR= 0.94, 95% CI: 0.65, 1.35) and cognitive impairment.

Further adjustment for lifestyle behaviours (smoking and alcohol in Model 4) slightly attenuated both associations between good (OR= 1.06, 95% CI: 0.81, 1.39) or poor oral health (OR= 0.94, 95% CI: 0.65, 1.35) and cognitive impairment.

Adjusting for depressive symptoms in the fully adjusted model (Model 5) had minimal impact on the association between good oral health and the subsequent cognitive impairment; however, it slightly attenuated the association between poor oral health and cognitive impairment (OR= 0.86, 95% CI: 0.60, 1.25).

In stratified samples into dentate and edentate (Table 7.3), the associations across all models remained non-significant. In Model 1 (unadjusted model), dentate participants who reported good oral health showed higher odds of cognitive impairment (OR= 1.20, 95% CI: 0.90 1.59) compared to those who reported poor oral health from the same group (i.e. dentate participants) (OR= 1.01, 95% CI: 0.69 1.48). On the same model for the edentate sample, participants who reported poor oral health (OR= 0.99, 95% CI: 0.46, 2.10) had higher odds of cognitive impairment compared to those who reported good oral health (OR= 0.85, 95% CI: 0.49, 1.46).

Another point to note is that the odds ratio (OR) of cognitive impairment for those who reported good oral health among dentate participants were higher than those who reported good oral health among edentate participants. For example, in the unadjusted models, the odds of having cognitive impairment among dentate participants who reported good oral health (OR= 1.20, 95% CI: 0.90, 1.59) was higher than edentate participants who reported good oral health (OR= 0.85, 95% CI: 0.49, 1.46). Through all adjusted models, the odds of cognitive impairment always remained higher among dentate compared to edentate only for those who reported good oral health.

On the other hand, the odds of cognitive impairment for those who reported poor oral health among edentate participants was higher than dentate participants after adjusting for covariates (Models 2 to 5). Only in the unadjusted model, the odds of cognitive impairment for dentate who reported poor oral health was higher than edentate. The rest of the models showed higher odds of cognitive impairment for edentate participants who reported poor oral health.

7.1.2 Edentulism and cognitive impairment

Edentulism at wave 3 was highly associated with higher odds of cognitive impairment at wave 8. In the unadjusted models, edentate participants were more likely to have cognitive impairment (OR= 4.06, 95% CI: 3.08, 5.36) compared to dentate participants.

The adjustment for demographic factors (age, sex and marital status in Model 2) attenuated almost 50% of the association; but edentate participants at wave 3 still had higher odds of a subsequent cognitive impairment (OR= 2.18, 95% CI: 1.60, 2.95) compared to dentate participants. Further adjustment of

socioeconomic factors (education and wealth in Model 3) attenuated the association substantially (OR= 1.57, 95% CI: 1.14, 2.16).

Furthermore, including lifestyle behaviours (smoking and alcohol in Model 4) did not cause a considerable change in the results. There was only a slight attenuation in the association between edentulism and cognitive impairment (OR= 1.54, 95% CI: 1.11, 2.13). In the fully adjusted model (Model 5), after adding depressive symptoms to the model, edentate participants still had significantly higher odds of cognitive impairment compared to dentate participants (OR= 1.53, 95% CI: 1.11, 2.12).

7.1.3 Oral impacts and cognitive impairment

Overall, for the oral impacts, participants who reported at least one oral impact at wave 3 had higher odds of cognitive impairment at wave 8 compared to those who reported none (Table 7.2). In the unadjusted model, participants who reported at least one oral impact were more likely to have cognitive impairment (OR= 1.77, 95% CI: 1.23, 2.53) compared to those who reported no oral impact.

Controlling for demographic factors (Model 2), slightly strengthened the association between oral impacts and cognitive impairment (OR= 1.80, 95% CI: 1.22, 2.63). Further adjusting for socioeconomic factors in model 3 again attenuated the association; however, it remained significant (OR= 1.66, 95% CI: 1.13, 2.45).

Moreover, including lifestyle behaviours (smoking and alcohol in Model 4) resulted in an additional attenuation to the model (OR= 1.61, 95% CI: 1.09, 2.37). Finally, adding depressive symptoms in the full model (Model 5) slightly attenuated the results but remained significant (OR= 1.49, 95% CI: 1.01–2.21).

Stratifying the sample according to teeth presence showed higher odds of cognitive impairment for those who reported oral impacts among dentate participants compared to edentate participants (Table 7.3).

In the opposite to what was observed in the whole sample and in the edentate sample, adjusting for demographic factors (Model 1) among dentate sample attenuated the association between oral impacts and the subsequent cognitive impairment (OR= 1.84, 95% CI: 1.19–2.85).

The associations between oral impacts and the subsequent cognitive impairment across all models among edentate participants were non-significant; while the associations were significant across all models among dentate participants.

Table 7.2 The longitudinal regression analysis of oral health at wave 3 and cognitive impairment at wave 8 (N=3,856), OR (95% CI)

Outcome: cognitive impairment	**Model 1** (Unadjusted)	**Model 2** (M1 +age, sex & marital status)	**Model 3** (M2 + education & wealth)	**Model 4** (M3+ smoking & alcohol)	**Model 5** (M4 + depressive symptoms)
Self-reported oral health					
Excellent (ref)					
Good	1.06 (0.83, 1.35)	1.15 (0.89, 1.49)	1.06 (0.81, 1.39)	1.04 (0.80, 1.36)	1.04 (0.79, 1.36)
Poor	0.93 (0.66, 1.29)	1.11 (0.78, 1.57)	0.94 (0.65, 1.35)	0.91 (0.63, 1.31)	0.86 (0.60, 1.25)
Edentulism					
Dentate (ref)					
Edentate	4.07*** (3.08, 5.36)	2.18*** (1.60, 2.95)	1.57** (1.14, 2.16)	1.54** (1.11, 2.13)	1.53** (1.11, 2.12)
Oral impacts					
No impact (ref)					
At least one impact	1.77** (1.23, 2.53)	1.80** (1.22, 2.63)	1.66* (1.13, 2.45)	1.61* (1.09, 2.37)	1.49* (1.01, 2.21)

p-value *<0.05, ** <0.01, ***<0.001

Table 7.3 The longitudinal regression analysis of oral health variables at wave 3 and cognitive impairment at wave 8 by edentulism (N=3,856), OR (95% CI)

Outcome: Cognitive Impairment	**Model 1** (Unadjusted)		**Model 2** (Model 1 +age, sex & marital status)		**Model 3** (Model 2 + education & wealth)		**Model 4** (Model 3+ smoking & alcohol)		**Model 5** (Model 4 + depressive symptoms)	
Dentate (n=3,501)										
Self-reported oral health										
Excellent (ref)										
Good	1.20	(0.90, 1.59)	1.26	(0.94, 1.69)	1.17	(0.87, 1.58)	1.16	(0.85, 1.56)	1.14	(0.84, 1.54)
Poor	1.01	(0.69, 1.48)	1.10	(0.74, 1.64)	0.94	(0.62, 1.41)	0.91	(0.61, 1.38)	0.86	(0.57, 1.30)
Oral impacts										
No impact (ref)										
At least one impact	1.88**	(1.25, 2.84)	1.84**	(1.19, 2.85)	1.73*	(1.11, 2.71)	1.69*	(1.08, 2.64)	1.58*	(1.00, 2.47)
Edentate (n=355)										
Self-reported oral health										
Excellent (ref)										
Good	0.85	(0.49, 1.46)	0.87	(0.48, 1.57)	0.81	(0.44, 1.49)	0.80	(0.43, 1.50)	0.84	(0.45, 1.57)
Poor	0.99	(0.46, 2.10)	1.68	(0.73, 3.86)	1.44	(0.60, 3.44)	1.41	(0.59, 3.41)	1.38	(0.57, 3.34)
Oral impacts										
No impact (ref)										
At least one impact	0.98	(0.46, 2.07)	1.24	(0.54, 2.81)	1.28	(0.56, 2.96)	1.22	(0.53, 2.83)	1.11	(0.48, 2.58)

p-value *<0.05, ** <0.01, ***<0.001

Summary

The results of the time-lag logistic regression showed that edentate participants or those who reported at least one oral impact at wave 3 had a higher probability of cognitive impairment 10 years later (wave 8). However, demographic and socioeconomic factors attenuated the association with edentulism substantially; while socioeconomic factors attenuated the association with oral impact only slightly. Dentate participants who reported at least one oral impact had higher odds of cognitive impairment and remained significant across all models of covariates adjustment. The analyses showed no significant association with self-reported oral health.

PATHWAY ANALYSIS OF THE ASSOCIATION BETWEEN ORAL HEALTH AT WAVE 3 AND COGNITIVE IMPAIRMENT AT WAVE 8

8 PATHWAY ANALYSIS OF THE ASSOCIATION BETWEEN ORAL HEALTH AT WAVE 3 AND COGNITIVE IMPAIRMENT AT WAVE 8

The previous chapter focused on the effect of oral health at baseline (wave 3) on cognitive impairment at wave 8 controlled for a variety of relevant factors. It showed that edentate participants were significantly more likely to have cognitive impairment after 10 years than participants who were dentate; however, the association was considerably attenuated by further adjustment for demographic and socioeconomic factors. The effect of oral impacts on cognitive impairment was significantly modified by edentulism. Dentate participants who reported oral impacts significantly had higher odds of having cognitive impairment after 10 years compared to dentate participants who reported no oral impacts. The association between self-reported oral health and cognitive impairment was not significant across all models.

The current chapter analyses different pathways of the association between oral health at wave 3 and cognitive impairment at wave 8. Section 8.1 presents the impact of inflammation, social isolation and nutrition at wave 6 in the association between edentulism at wave 3 and cognitive impairment at wave 8. Section 8.2 presents the impact of the same mediators in the association between oral impacts at wave 3 and cognitive impairment at wave 8. Section 8.3 presents the role of inflammations at wave 2 as a precursor in the association between edentulism at wave 3 and cognitive impairment at wave 8.

Inflammation in section 8.1 and 8.2 was considered as a latent variable for three inflammatory markers obtained from wave 6: C-Reactive Protein (CRP), White Blood cell Count (WBC), and plasma fibrinogen. In section 8.3, given that there were no data for the WBC in wave 2; it was not possible to create a latent variable for that analysis. Instead, the CRP and fibrinogen were included as separate markers of inflammation.

A detailed description of the variables used in the pathway analysis was presented in Chapter 3 (Methodology). In brief, nutrition pathway was assessed by the total number of fruit and vegetable portions consumed every day, and the social isolation was assessed by an index which included the level of contact with the participant’s social network and the involvement in social organisations. Both variables were used as mediators from wave 6.

Structural Equation Modelling using Mplus software was used to find the direct and indirect effect estimates of each pathway. Model 1 included the exposure, the outcome, and mediators without any adjustment; while Model 2 included the same variables plus age and sex at wave 3.

The curved lines in Figures 8.1 to 8.6 represent unanalysed associations. A box designates measured variables, and oval represents the latent variable. Curved lines with arrowheads at both ends represent covariances or correlations between exogenous variables. The straight lines with an arrowhead pointing from the causal variable toward the effect variable represent the pathways. The yellow highlighted lines in all figures represent a significant pathway on the level *p*-value ≤0.05.

8.1 The association between edentulism and cognitive impairment mediated by nutrition, social isolation and inflammation

Edentate participants at wave 3 had significantly higher odds of cognitive impairment 10-years later, as shown in the previous chapter. In this section, the mechanism of that relationship through inflammatory, social, and nutritional pathways will be investigated, as shown in Figure 8.1 and Table 8.1 (Model 1).

It showed that edentate participants at wave 3 also had higher estimates of cognitive impairment at wave 8 (β= 0.66, Standard Error (SE): 0.09, *p*-value <0.001); confirming the previous findings. The sum of the indirect effects, which is the total indirect effects of the three pathways (inflammatory, social and nutritional), from edentulism to cognitive impairment was significant (β= 0.10, SE: 0.03, *p*-value <0.001).

Controlling for age and sex (Figure 8.2 and Table 8.2) in Model 2 attenuated the direct association between edentulism at wave 3 and cognitive impairment at wave 8 (β=0.39, SE: 0.09, *p*-value<0.001). The sum of indirect effect from edentulism to cognitive impairment through all mediators remained significant after controlling for age and sex.

8.1.1 Edentulism - nutrition - cognitive impairment

The results of the unadjusted model (Model 1, Table 8.1) showed that edentate participants at wave 3 compared to dentate participants consumed less fruits and vegetables at wave 6 (β= -0.52, SE: 0.14, *p*-value <0.001). The association between nutrition and cognitive impairment was small and non-significant (β= 0.02, SE: 0.01, *p*-value= 0.143). The indirect effect through nutrition was negative but non-significant (β= -0.01, SE: 0.01, *p*-value= 0.171).

After adjusting for age and sex in Model 2 (Figure 8.2 and Table 8.2), the association between edentulism and nutrition was strengthened (β= -0.64, SE: 0.14, *p*-value <0.001). The association between nutrition and cognitive impairment remained non-significant (β= 0.01, SE: 0.01, *p*-value= 0.265). The indirect effect through nutrition remained non-significant after adjusting for age and sex (β= -0.01, SE: 0.01, *p*-value= 0.278).

8.1.2 Edentulism - social isolation - cognitive impairment

Edentate participants at wave 3 were more socially isolated (β= 0.45, SE: 0.09, *p*-value <0.001). The results also showed that participants who were more socially isolated were significantly more likely to have cognitive impairment (β= 0.15, SE: 0.05, *p*-value= 0.001). The indirect effect from edentulism to cognitive impairment through social isolation was significant (β= 0.07, SE: 0.02, *p*-value= 0.006).

Controlling for age and sex in Model 2 all the direct and indirect associations. The association between edentulism and social isolation was attenuated slightly but remained significant (β= 0.32, SE: 0.09, *p*-value <0.001). Moreover, the association between social isolation and cognitive impairment got attenuated as well (β= 0.11, SE: 0.05, *p*-value= 0.018). The indirect effect through social isolation also got attenuated but remained significant (β= 0.04, SE: 0.02, *p*-value= 0.049).

8.1.3 Edentulism - inflammation - cognitive impairment

Edentate participants at wave 3 had higher inflammation at wave 6 (β= 0.42, SE: 0.09, *p*-value <0.001). The direct effect of the latent variable of inflammatory markers at wave 3 on cognitive impairment at wave 8 was significant (β= 0.08, SE: 0.04, *p*-value= 0.033). So for each unit increase inflammation latent variable, cognitive impairment increases by 0.08. The indirect effect of edentulism to

cognitive impairment through inflammation was weaker than the direct effect and fell short of significance (β= 0.03, SE: 0.02, *p*-value= 0.051).

After controlling for age and sex, the association between edentulism and inflammation was attemuated (β= 0.27, SE: 0.09, *p*-value =0.003). The direct effect of inflammation on cognitive impairment became non-significant (β= 0.06, SE: 0.04, *p*-value= 0.102). Also the the indirect effect of inflammation in the association between edentulism and cognitive impairment became non-significant (β= 0.03, SE: 0.01, *p*-value= 0.152).

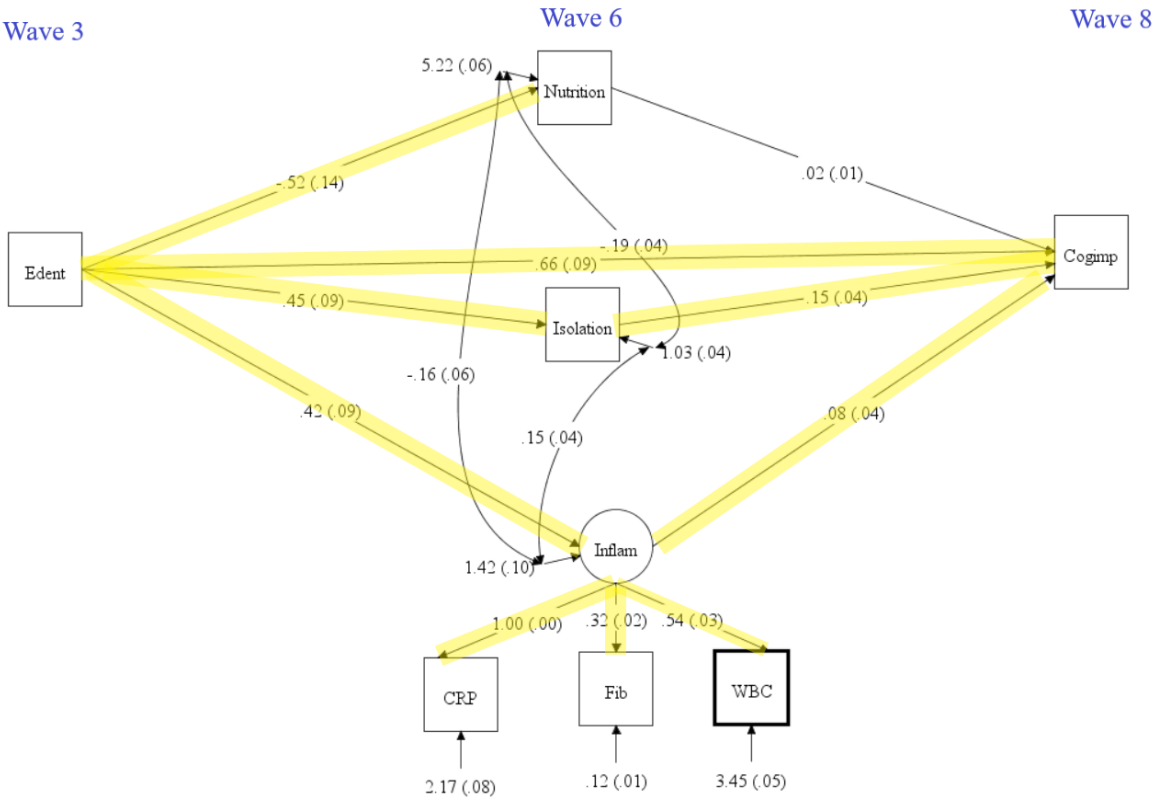

Figure 8.1 SEM path diagram of the unadjusted association between edentulism at wave 3 and cognitive impairment at wave 8 mediated by nutrition, social isolation and inflammation at wave 6 (Model 1), β coefficients (SE). Highlighted path lines represent significant associations

Table 8.1 SEM output of the unadjusted association between edentulism at wave 3 and cognitive impairment at wave 8 mediated by inflammation, social isolation and nutrition at wave 6 (Model 1), β(SE) (n= 3,856)

	β (SE)	***p*-value**
Latent variable for inflammation		
BY CRP [1]	1.00 (0.00)	999
BY Fibrinogen	0.32 (0.02)	<0.001
BY WBC [2]	0.54 (0.03)	<0.001
Direct effects		
Edentulism → Nutrition	-0.52(0.14)	<0.001
Edentulism → Social isolation	0.45 (0.09)	<0.001
Edentulism → Inflammation	0.42 (0.09)	<0.001
Nutrition→ Cognitive impairment	0.02 (0.01)	0.143
Social isolation→ Cognitive impairment	0.15 (0.05)	0.001
Edentulism → Cognitive impairment	0.66 (0.09)	<0.001
Inflammation → Cognitive impairment	0.08 (0.04)	0.033
Intercepts		
Social isolation	2.15 (0.10)	<0.001
Nutrition	5.72 (0.16)	<0.001
CRP	1.55 (0.15)	<0.001
Fibrinogen	2.84 (0.04)	<0.001
WBC	6.14 (0.14)	<0.001
Indirect effects		
Edentulism to cognitive impairment		
Sum of indirect effect	0.10 (0.03)	0.001
Edentulism → nutrition → cognitive impairment	-0.01(0.01)	0.171
Edentulism → social isolation → cognitive impairment	0.07 (0.02)	0.006
Edentulism → inflammation → cognitive impairment	0.03 (0.02)	0.051
Measuring Model Fit		
CFI[3]	0.996	
TLI[4]	0.989	
RMSEA[5]	0.015	
SRMR[6]	0.019	

[1] C- reactive Protein
[2] White Blood Cells
[3] Comparative Fit Index
[4] Tucker-Lewis Index
[5] Root Mean Square Error of Approximation
[6] Standardised Root Mean Square Residual

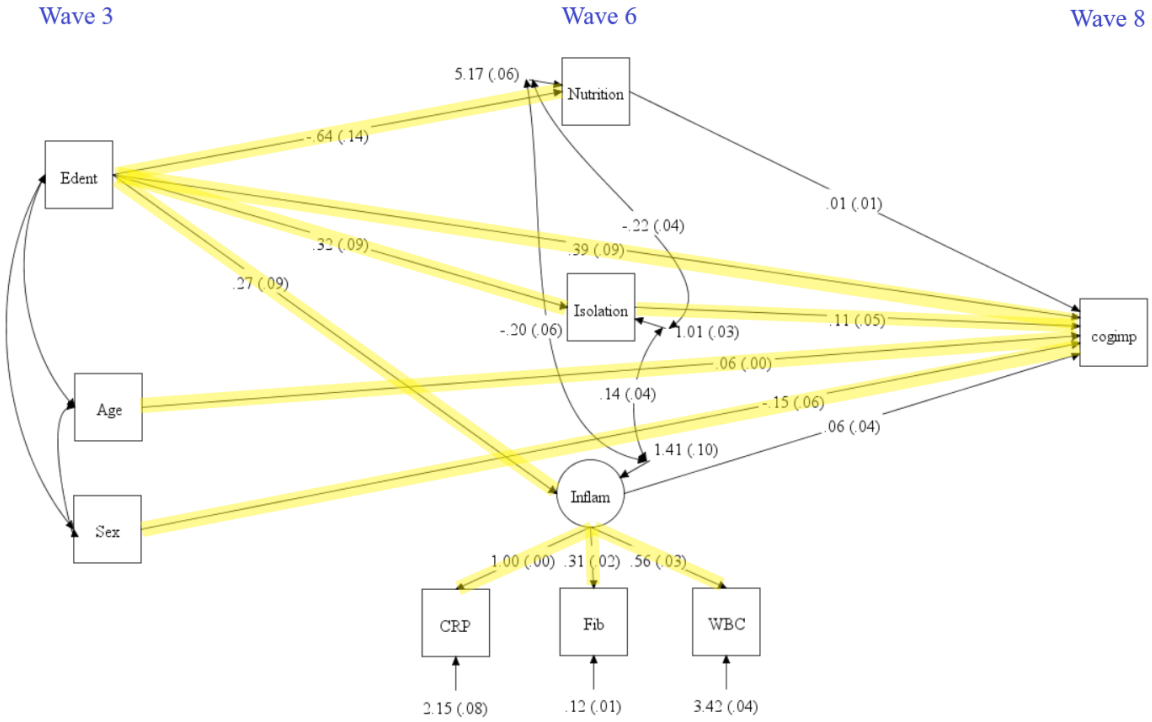

Figure 8.2 SEM path diagram of the age- and sex-adjusted association between edentulism at wave 3 and cognitive impairment at wave 8 mediated by nutrition, social isolation and inflammation at wave 6 (Model 2), β coefficients (SE). Highlighted path lines represent significant associations

Table 8.2 SEM output of the age- and sex-adjusted association between edentulism at wave 3 and cognitive impairment at wave 8 mediated by inflammation, social isolation and nutrition at wave 6, (Model 2), β(SE) (n= 3,856)

	β (SE)	***p*-value**
Latent variable for inflammation		
BY CRP [1]	1.00 (0.00)	999
BY Fibrinogen	0.31 (0.02)	<0.001
BY WBC [2]	0.56 (0.03)	<0.001
Direct effects		
Edentulism → Nutrition	-0.64(0.14)	<0.001
Edentulism → Social isolation	0.32 (0.09)	<0.001
Edentulism → Inflammation	0.27 (0.09)	0.003
Edentulism → Cognitive impairment	0.39 (0.09)	<0.001
Inflammation → Cognitive impairment	0.06 (0.04)	0.102
Social isolation → Cognitive impairment	0.11 (0.05)	0.018
Nutrition → Cognitive impairment	0.01 (0.01)	0.265
Age → Cognitive impairment	0.06 (0.004)	<0.001
Sex → Cognitive impairment	-0.15(0.06)	0.020
Intercepts		
Social isolation	1.01 (0.22)	<0.001
Nutrition	4.39 (0.34)	<0.001
CRP	0.59 (0.33)	0.074
Fibrinogen	2.25 (0.09)	<0.001
WBC	5.91 (0.33)	<0.001
Indirect effects		
Edentulism to cognitive impairment		
Sum of indirect effect	0.04 (0.02)	0.043
Edentulism → nutrition → cognitive impairment	-0.01(0.01)	0.278
Edentulism → social isolation → cognitive impairment	0.04 (0.02)	0.049
Edentulism → inflammation → cognitive impairment	0.02 (0.01)	0.152
Measuring Model Fit		
CFI[3]	0.911	
TLI[4]	0.837	
RMSEA[5]	0.050	
SRMR[6]	0.299	

[1] C- reactive Protein
[2] White Blood Cells
[3] Comparative Fit Index
[4] Tucker-Lewis Index
[5] Root Mean Square Error of Approximation
[6] Standardized Root Mean Square Residual

8.2 Oral impacts and cognitive impairment mediated by nutrition, social isolation and inflammation

The direct effect of oral impact at wave 3 on cognitive impairment at wave 8 was significant in the unadjusted model, Table 8.3 and Figure 8.3 (β= 0.25, SE: 0.10, p-value= 0.01). Also, the sum of indirect effects of all pathways for the association between oral impacts and cognitive impairment was significant (β= 0.05, SE: 0.12, p-value= 0.041).

After adjusting for age and sex in Model 2 (Figure 8.4 and Table 8.4), the direct effect of oral impact on cognitive impairment did not change much from the unadjusted model (β= 0.28, SE: 0.10, p-value= 0.007). The sum of the indirect effects of all pathways, which swas already marginal, became non-significant (β= 0.03, SE: 0.02, p-value= 0.089).

8.2.1 Oral impacts - nutrition - cognitive impairment

In the unadjusted model (Table 8.3), participants who reported oral impacts at wave 3, had lower nutrition at wave 6 (β= -0.23, SE: 0.14, p-value= 0.095); although that association was not significant. Likewise, the association between nutrition and cognitive impairment was not significant (β= 0.01, SE: 0.01, p-value= 0.384). The indirect association between oral impacts and cognitive impairment through nutrition was not significant as well (β= -0.002, SE: 0.003, p-value= 0.440). After adjusting for age and sex (Table 8.4), the associations did not considerably change and remained non-significant.

8.2.2 Oral impacts - social isolation - cognitive impairment

The association between oral impacts and social isolation, in the unadjusted model (Table 8.3), was not significant (β= 0.17, SE: 0.10, p-value= 0.101). On the other hand, the more socially isolated participants at wave 6 had higher estimates of cognitive impairment at wave 8 (β= 0.17, SE: 0.04, p-value <0.001). The indirect effect of social isolation in the association between oral impacts and cognitive impairment was not significant (β= 0.03, SE: 0.02, p-value =0.130).

Including age and sex to the model (Figure 8.4 and Table 8.4) slightly attenuated the associations between oral impacts and social isolation (β= 0.15, SE: 0.10, p-value= 0.136); yet remained non-significant, and the association between social isolation and cognitive impairment (β= 0.12, SE: 0.05, p-value= 0.009). Lastly, the indirect effect of social isolation in the association between oral impacts and cognitive impairment did not considerably change by adjusting for age and sex and remained non-significant (β= 0.02, SE: 0.01, p-value= 0.196).

8.2.3 Oral impacts - inflammation - cogntive impairment

As shown in Model 1 (Table 8.3), participants who reported oral impacts at wave 3 had higher inflammation at wave 6 (β= 0.22, SE: 0.11, p-value= 0.043); and those who had higher inflammation, had also higher estimates of cognitive impairment (β= 0.09, SE: 0.04, p-value= 0.016). However, the indirect effect of inflammation in the association between oral impacts and cognitive impairment was not significant (β= 0.02, SE: 0.01, p-value= 0.119).

In Model 2 (Table 8.4), controlling for age and sex slightly attenuated the association between oral impacts and inflammation (β= 0.21, SE: 0.11, p-value= 0.054) and became marginally non-significant. Also, the association between inflammation and cognitive impairment became non-significant after controlling for age and sex (β= 0.06, SE: 0.04, p-value= 0.102). The indirect effect of inflammation in the association between oral impacts and cognitive impairment did not substantially change after contolling for age and sex (β= 0.01, SE: 0.01, p-value= 0.212).

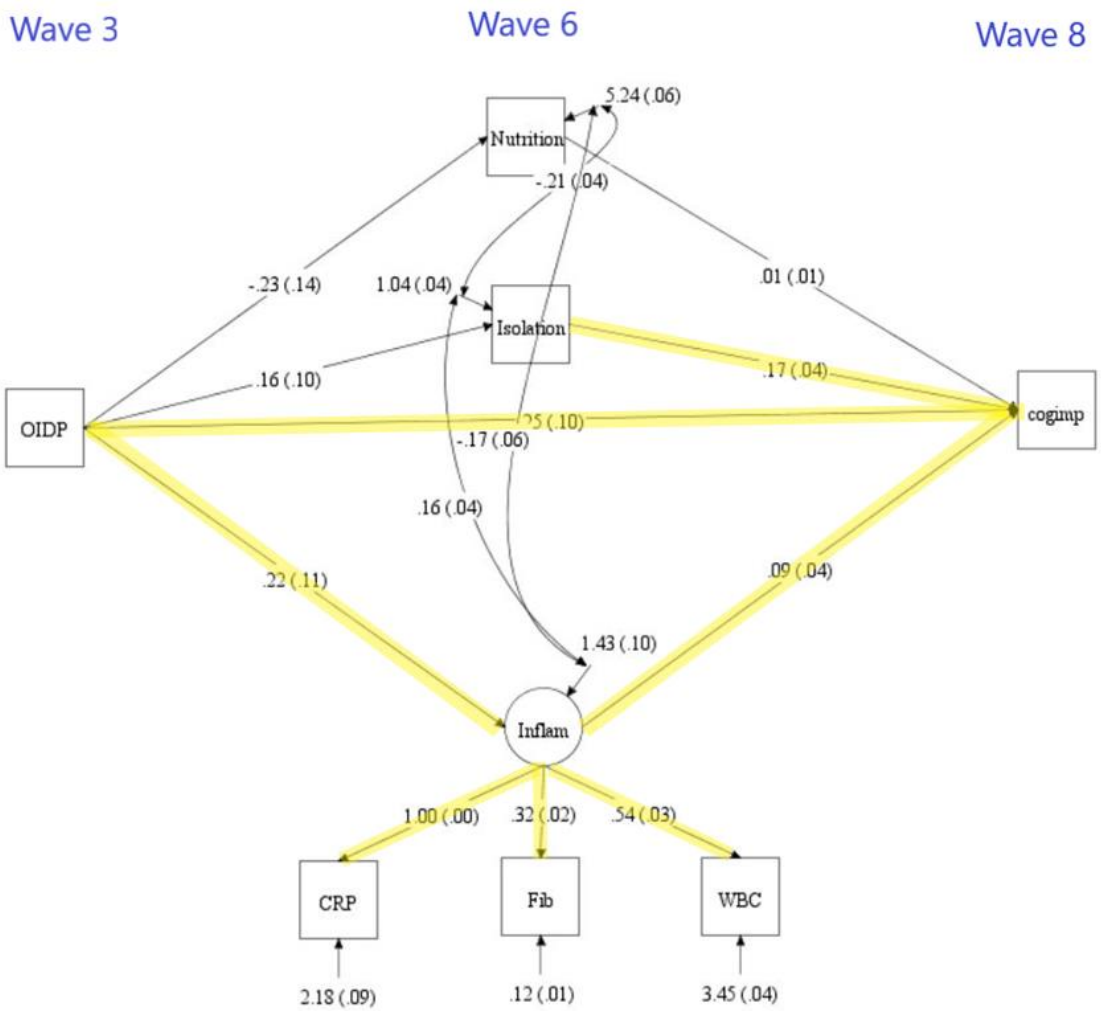

Figure 8.3 SEM path diagram of the unadjusted association between oral impacts at wave 3 and cognitive impairment at wave 8 mediated by nutrition, social isolation and inflammation at wave 6 (Model 1), β(SE). Highlighted path lines represent significant associations

Table 8.3 SEM output of the unadjusted association between oral impacts at wave 3 and cognitive impairment at wave 8 mediated by inflammation, social isolation and nutrition at wave 6 (Model 1), β(SE) (n= 3,856)

	β (SE)	***p*-value**
Latent variable for inflammation		
BY CRP [1]	1.00 (0.00)	999
BY Fibrinogen	0.32 (0.02)	<0.001
BY WBC [2]	0.54 (0.03)	<0.001
Direct effects		
Oral impacts → Nutrition	-0.23(0.14)	0.095
Oral impacts → Social isolation	0.17 (0.10)	0.101
Oral impacts → Inflammation	0.22 (0.11)	0.043
Oral impacts → Cognitive impairment	0.25 (0.10)	0.01
Inflammation → Cognitive impairment	0.09 (0.04)	0.016
Social isolation → Cognitive impairment	0.17 (0.04)	<0.001
Nutrition → Cognitive impairment	0.01 (0.01)	0.384
Intercepts		
Social isolation	2.62 (0.03)	<0.001
Nutrition	5.17 (0.04)	<0.001
CRP	2.09 (0.06)	<0.001
Fibrinogen	2.95 (0.01)	<0.001
WBC	6.41 (0.05)	<0.001
Indirect effects		
Oral impacts to cognitive impairment		
Sum of indirect effect	0.05 (0.02)	0.041
Oral impacts → Nutrition → Cognitive impairment	-0.002 (0.003)	0.440
Oral impacts → Social isolation → Cognitive impairment	0.03 (0.02)	0.130
Oral impacts → Inflammation → Cognitive impairment	0.02 (0.01)	0.119
Measuring Model Fit		
CFI[3]	0.997	
TLI[4]	0.991	
RMSEA[5]	0.013	
SRMR[6]	0.011	

[1] C- reactive Protein
[2] White Blood Cells
[3] Comparative Fit Index
[4] Tucker-Lewis Index
[5] Root Mean Square Error of Approximation
[6] Standardized Root Mean Square Residual

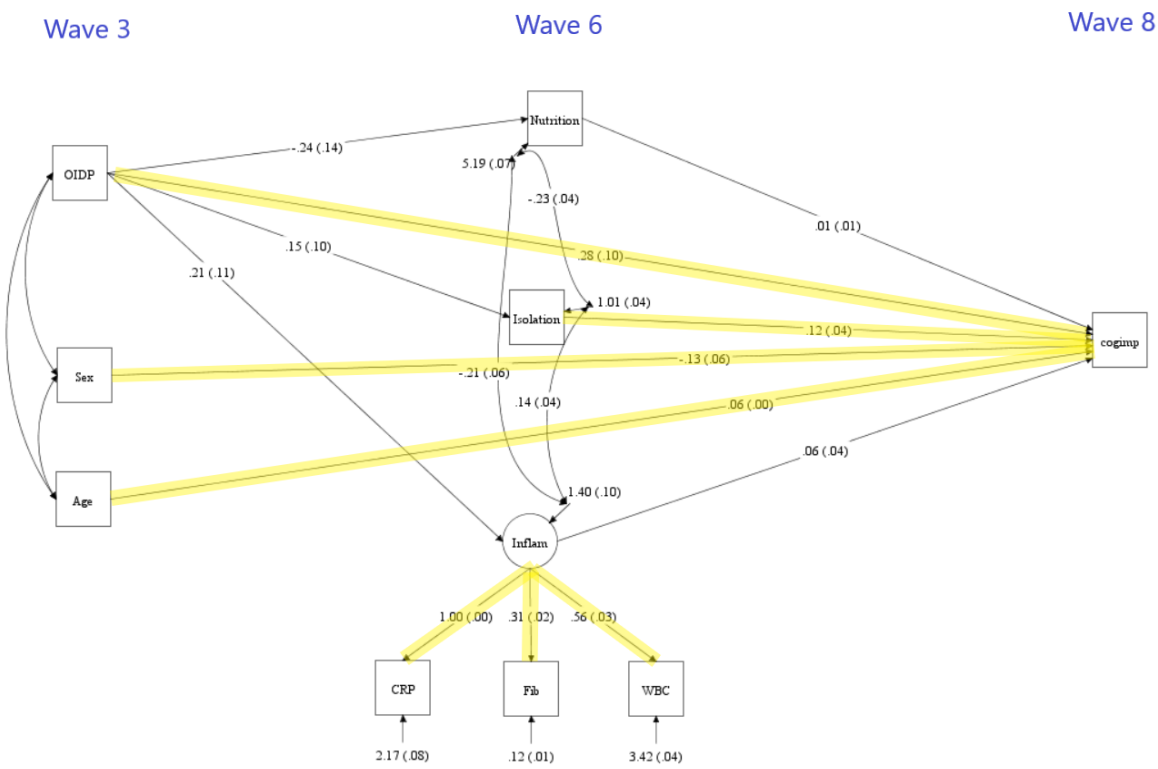

Figure 8.4 SEM path diagram of the age- and sex-adjusted association between oral impacts at wave 3 and cognitive impairment at wave 8 mediated by nutrition, social isolation and inflammation at wave 6 (Model 1), β(SE). Highlighted path lines represent significant associations

Table 8.4 SEM output of the age- and sex-adjusted association between edentulism at wave 3 and cognitive impairment at wave 8 mediated by inflammation, social isolation and nutrition at wave 6 (Model 2), β(SE) (n= 3,856)

	β (SE)	***p*-value**
Latent variable for inflammation		
BY CRP [1]	1.00 (0.00)	999
BY Fibrinogen	0.31 (0.02)	<0.001
BY WBC [2]	0.56 (0.03)	<0.001
Direct effects		
Oral impacts → Nutrition	-0.24 (0.14)	0.076
Oral impacts → Social isolation	0.15 (0.10)	0.136
Oral impacts → Inflammation	0.21 (0.11)	0.054
Oral impacts → Cognitive impairment	0.28 (0.10)	0.007
Inflammation → Cognitive impairment	0.06 (0.04)	0.102
Social isolation → Cognitive impairment	0.12 (0.05)	0.009
Nutrition → Cognitive impairment	0.01 (0.01)	0.48
Age → Cognitive impairment	0.06 (0.00)	<0.001
Sex → Cognitive impairment	-0.13 (0.06)	0.038
Intercepts		
Social isolation	1.19 (0.22)	<0.001
Nutrition	2.27 (0.09)	<0.001
CRP	0.80 (0.33)	0.014
Fibrinogen	2.27 (0.09)	<0.001
WBC	6.03 (0.33)	<0.001
Indirect effects		
Oral impacts to cognitive impairment		
Sum of indirect effect	0.03 (0.02)	0.089
Oral impacts → Nutrition → Cognitive impairment	-0.002 (0.003)	0.511
Oral impacts → Social isolation → Cognitive impairment	0.02 (0.01)	0.196
Oral impacts → Inflammation → Cognitive impairment	0.01 (0.01)	0.212
Measuring Model Fit		
CFI[3]	0.904	
TLI[4]	0.824	
RMSEA[5]	0.052	
SRMR[6]	0.322	

[1] C- reactive Protein
[2] White Blood Cells
[3] Comparative Fit Index
[4] Tucker-Lewis Index
[5] Root Mean Square Error of Approximation
[6] Standardized Root Mean Square Residual

8.3 The role of inflammatory markers preceding the association between edentulism and cognitive impairment

Figure 8.5 and Table 8.5 are summarising the results of the SEM of the effect of inflammatory markers (fibrinogen and CRP) at wave 2 on cognitive impairment at wave 8 mediated by edentulism at wave 3, social isolation and nutrition at wave 6. Figure 8.6 and Table 8.6 presents the same associations after controlling for age and sex at wave 3. Four different pathways will be presented:

1. Fibrinogen – edentulism – social isolation – cognitive impairment
2. Fibrinogen – edentulism – nutrition – cognitive impairment
3. CRP – edentulism – social isolation – cognitive impairment
4. CRP – edentulism – nutrition – cognitive impairment

The results of the unadjusted models will be presented first in each pathway. Then the results of the age and sex-adjusted models will follow.

8.3.1 Fibrinogen – edentulism – social isolation – cognitive impairment

In the unadjusted model (Table 8.5), the direct association between fibrinogen at wave 2 and cognitive impairment wave 8 was significant (β= 0.15, SE: 0.07, *p*-value =0.028). Also, fibrinogen at wave 2 showed to be significantly preceding edentulism at wave 3 (β= 0.14, SE: 0.06, *p*-value =0.024). Also, the indirect effect of edentulism in the association between fibrinogen and cognitive impairment was significant (β= 0.05, SE: 0.02, *p*-value =0.034). So for each unit increase in fibrinogen, the estimate of cognitive impairment increased by 0.05 due to the indirect effect of edentulism.

Additionally, those who were edentate at wave 3, had higher estimates of social isolation at wave 6, (β= 0.18, SE: 0.05, *p*-value <0.001). The direct association between fibrinogen and social isolation was not significant (β= 0.10, SE: 0.06, *p*-value =0.077), and the indirect association between fibrinogen and social isolation through edentulism was marginally non-significant (β= 0.03, SE: 0.01, *p*-value =0.051).

Moreover, the SEM model showed that socially isolated participants at wave 6, had higher estimates of cognitive impairment at wave 8 (β= 0.14, SE: 0.06, *p*-value =0.020). The results also showed that edentate participants at wave 3 had significantly higher estimates of cognitive impairment (β= 0.34, SE: 0.05, *p*-value <0.001). Likewise, the indirect effect of social isolation in the association between edentulism and cognitive impairment was significant (β= 0.02, SE: 0.01, *p*-value =0.042).

The sum of the indirect effects of edentulism, social isolation and nutrition in the pathway from fibrinogen to cognitive impairment was significant (β= 0.05, SE: 0.02, *p*-value =0.032). The effect of edentulism in the same pathway (from fibrinogen to cognitive impairment) was the only specific significant indirect effect. Including either social isolation or nutrition to the pathway changed the indirect effect to be non-significant.

After adjusting for age and sex in Model 2 (Table 8.6), the direct impact of fibrinogen at wave 2 on cognitive impairment at wave 8 became non-significant (β= 0.12, SE: 0.07, *p*-value =0.103). Likewise, the direct impact of fibrinogen on edentulism became non-significant (β= 0.06, SE: 0.07, *p*-value =0.423). The indirect effect of edentulism in the association between fibrinoge and cognitive impairment became non-significant (β= 0.01, SE: 0.02, *p*-value =0.436).

In Model 2 (age and sex-adjusted), the direct impact of fibrinogen at wave 2 or edentulism at wave 3 on social isolation at wave 6 did not substantially change. The indirect effect of edentulism in the association between fibrinogen and social isolation did not change considerably and remained non-significant (β= 0.01, SE: 0.01, *p*-value =0.428). Additionally, the association between social isolation and cognitive impairment became marginally non-significant (β= 0.11, SE: 0.06, *p*-value =0.077). Also, the indirect effect of social isolation in the association between edentulism and cognitive impairment became non-significant after age and sex adjustment (β= 0.02, SE: 0.01, *p*-value =0.098). Moreover, the sum of the indirect effects of edentulism, social isolation and nutrition in the pathway from

fibrinogen to cognitive impairment became non-significant (β= 0.01, SE: 0.02, *p*-value =0.433).

In summary, fibrinogen significantly preceded the association between edentulism and cognitive impairment; although that effect became non-significant after age and sex adjustment. Including nutrition and social isolation to the same pathway showed no significant impact of fibrinogen preceding the association between edentulism and cognitive impairment in all models.

8.3.2 Fibrinogen – edentulism – nutrition – cognitive impairment

The association between fibrinogen at wave 2 and nutrition at wave 6 was not signficant (β= -0.08, SE: 0.09, *p*-value =0.410); and the indirect effect of edentulism in that association was marginally not significant (β= -0.04, SE: 0.02, *p*-value =0.072) (Table 8.5). Including nutrition in the association beween edentulism and cognitive impairment preceded by fibrinogen resulted in a non-significant estimate (β= -0.001, SE: 0.001, *p*-value =0.200).

Furthermore, the direct impact of edentulism on nutrition was significant (β= -0.27, SE: 0.10, *p*-value =0.003). So, edentate participants at wave 3 had significantly lower nutrition estimate compared to dentate participants. Additionally, the association between nutrition and cognitive impairment was also significant (β= 0.03, SE: 0.02, *p*-value =0.032). On the other hand, the indirect effect of nutrition in the association between edentulism and cognitive impairment was not significant (β= -0.01, SE: 0.005, *p*-value =0.123).

In model 2 (Table 8.6), although the association between fibrinogen and nutrition remained non-significant, the association got strengthened (β= -0.15, SE: 0.10, *p*-value =0.131). The indirect association between fibrinogen and nutrition through edentulism got attenuated and remained non-significant. The role of fibrinogen as a precursor in the association between edentulism and cognitive impairment mediated by nutrition remained non-significant and did not change in this model.

More in Model 2, the association between edentulism and nutrition got attenuated after age and sex adjustment; however, it remained significant (β= -0.17, SE: 0.08, *p*-value =0.023). On the other hand, the association between edentulism and cognitive impairment became non-significant by adding age and sex to the model (β= 0.03, SE: 0.02, *p*-value =0.072). The indirect association between edentulism and cognitive impairment through nutrition did no change and remained non-significant.

8.3.3 CRP – edentulism – social isolation – cognitive impairment

Unlike the association between fibrinogen and cognitive impairment, the direct association between CRP at wave 2 and cognitive impairment at wave 8 was negative and non-significant (β= -0.03, SE: 0.02, *p*-value =0.114). On the other hand, the association between CRP and edentulism (β= 0.05, SE: 0.02, p-value =0.004) was similar to the results observed in fibrinogen. However, the association with CRP was smaller. So, for each unit increase in CRP at wave 2, the estimates of edentulism at wave 3 increase by 0.05. The indirect effect of edentulism in the association between CRP and cognitive impairment was significant (β= 0.02, SE: 0.007, *p*-value =0.009). So, for each unit increase in CRP at wave 2, the estimate of cognitive impairment at wave 8 increased by 0.02 as the result of the indirect effect of edentulism at wave 3.

Although the direct association between CRP and social isolation was not significant (β= 0.02, SE: 0.02, *p*-value =0.285); the indirect association between CRP and social isolation through edentulism was significant (β= 0.01, SE: 0.004, *p*-value =0.022). So, for each unit increase in CRP at wave 2, the estimate of social isolation at wave 6 significantly increase by 0.01 because of the indirect effect of edentulism at wave 3.

The sum of the indirect effects of edentulism, social isolation and nutrition in the pathway from CRP to cognitive impairment was significant (β= 0.02, SE: 0.007, *p*-value =0.008); however, the sum of indirect effects was much smaller than the results in fibrinogen. Including either social isolation or nutrition to the pathway changed the indirect effect to be non-significant.

In Model 2 (age and sex-adjusted), the direct impact of CRP on cognitive impairment did not considerably change and remained negative and non-significant. Also, adjusting for age and sex did not have any considerable effect on the direct association between CRP and edentulism. The indirect effect of edentulism in the association between CRP and cognitive impairment got attenuated in this model yet remained significant (β= 0.01, SE: 0.01, *p*-value =0.032).

Moreover, although the direct association between CRP and social isolation get attenuated after age and sex adjustment (β= 0.01, SE: 0.02, *p*-value =0.426); the indirect association through edentulism did not considerably change and remained significant (β= 0.01, SE: 0.004, *p*-value =0.018).

The sum of indirect effects, edentulism at wave 3 or edentulism plus social isolation or nutrition at wave 6, in the association between CRP at wave 2 and cognitive impairment at wave 8 got attenuated after adjusting for age and sex; however, it remained significant (β= 0.01, SE: 0.01, *p*-value =0.023).

8.3.4 CRP – edentulism – nutrition – cognitive impairment

The direct association between CRP and nutrition was not-significant (β= -0.04, SE: 0.03, *p*-value =0.205); which was similar to what was in fibrinogen (Table 8.5). On the other hand, the indirect effect of edentulism in the association between CRP and nutrition was significant (β= -0.01, SE: 0.007, *p*-value =0.040). Including nutrition in the association between edentulism and cognitive impairment preceded by CRP resulted in a minimal and non-significant estimate (β= <0.001, SE: <0.001, *p*-value =0.172).

The association between CRP and nutrition in Model 2 (age and sex-adjusted) remained without any considerable change and non-significant. On the other hand, the indirect association between CRP and nutrition through edentulism became non-significant after adjusting for age and sex (β= -0.01, SE: 0.01, *p*-value =0.080). The role of CRP as a precursor in the

association between edentulism and cognitive impairment mediated by nutrition did not change and remained non-significant and in this model.

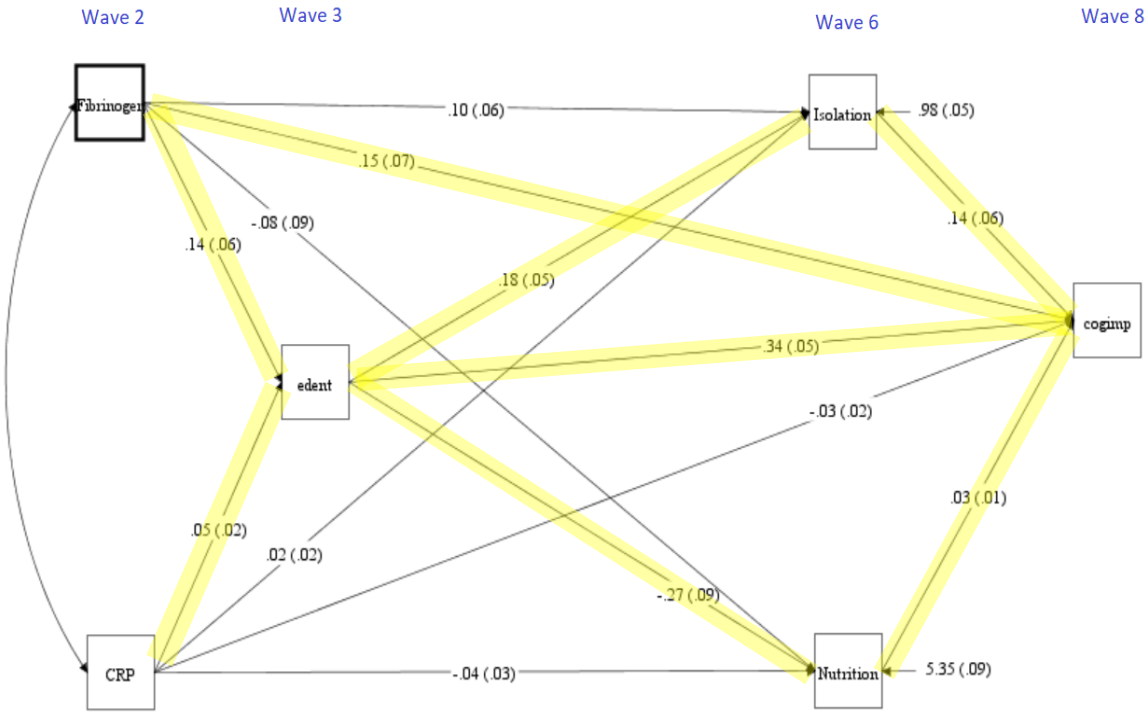

Figure 8.5 SEM path diagram of the unadjusted association between edentulism at wave 3 and cognitive impairment at wave 8 preceded by inflammatory markers (fibrinogen and CRP) at wave 2 and mediated by nutrition and social isolation at wave 6 (Model 1), β coefficients (SE). Highlighted path lines represent significant associations

Table 8.5 SEM output of the unadjusted association between edentulism at wave 3 and cognitive impairment at wave 8 preceded by inflammatory markers (fibrinogen and CRP) and mediated by inflammation, social isolation and nutrition at wave 6 (Model 1), β(SE) (n= 3,856)

	β (SE)	***p*-value**
Direct effects		
Fibrinogen → Edentulism	0.14 (0.06)	0.024
CRP[1] → Edentulism	0.05 (0.02)	0.004
Edentulism → Social isolation	0.18 (0.05)	<0.001
Fibrinogen → Social isolation	0.10 (0.06)	0.077
CRP → Social isolation	0.02 (0.016)	0.285
Edentulism→ Nutrition	-0.27 (0.10)	0.003
Fibrinogen → Nutrition	-0.08 (0.09)	0.410
CRP → Nutrition	-0.04 (0.03)	0.205
Edentulism → Cognitive impairment	0.34 (0.05)	<0.001
Social isolation → Cognitive impairment	0.14 (0.06)	0.020
Nutrition → Cognitive impairment	0.03 (0.02)	0.032
Fibrinogen → Cognitive impairment	0.15 (0.07)	0.028
CRP → Cognitive impairment	-0.03 (0.02)	0.114
Intercepts		
Social isolation	0.98 (0.05)	<0.001
Nutrition	5.35 (0.09)	<0.001
Indirect effects		
Fibrinogen → Edentulism → nutrition	-0.04 (0.02)	0.072
CRP → Edentulism → nutrition	-0.01 (0.007)	0.040
Fibrinogen→ Edentulism → Social isolation	0.03 (0.01)	0.051
CRP → Edentulism →Social isolation	0.01 (0.004)	0.022
Edentulism to cognitive impairment		
Sum of indirect effect	0.02 (0.01)	0.239
Edentulism → social isolation → cognitive impairment	0.02 (0.01)	0.042
Edentulism → nutrition → cognitive impairment	-0.01 (0.005)	0.123
Fibrinogen to cognitive impairment		
Sum of indirect effect	0.05 (0.02)	0.032
Fibrinogen → Edentulism → social isolation → cognitive impairment	0.003 (0.002)	0.130
Fibrinogen → Edentulism → nutrition → cognitive impairment	-0.001 (0.001)	0.200
Fibrinogen → Edentulism → cognitive impairment	0.05 (0.02)	0.034
CRP to cognitive impairment		
Sum of indirect effect	0.02 (0.007)	0.008
CRP → edentulism → social isolation → cognitive impairment	0.001 (0.001)	0.097
CRP → edentulism → nutrition → cognitive impairment	<0.001 (<0.001)	0.172
CRP → edentulism → cognitive impairment	0.02 (0.007)	0.009
Measuring Model Fit		
CFI[2]	0.989	
TLI[3]	0.845	
RMSEA[4]	0.022	
SRMR[5]	0.008	

[1] C- reactive Protein
[2] Comparative Fit Index
[3] Tucker-Lewis Index
[4] Root Mean Square Error of Approximation
[5] Standardised Root Mean Square Residual

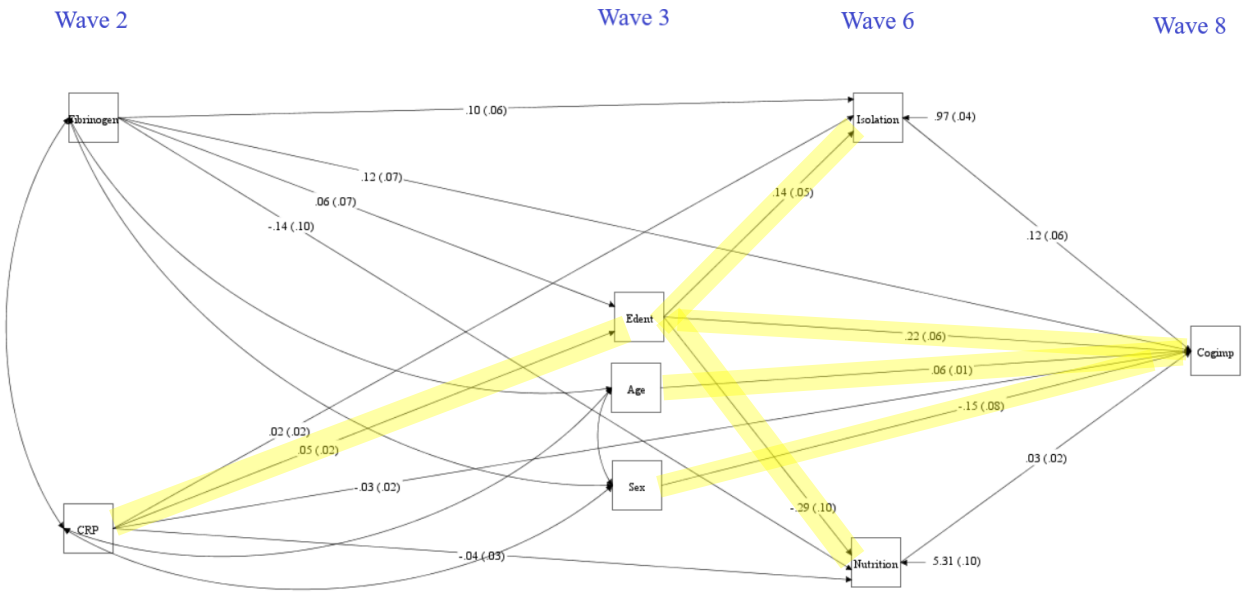

Figure 8.6 SEM path diagram of the age- and sex-adjusted association between edentulism at wave 3 and cognitive impairment at wave 8 preceded by inflammatory markers (fibrinogen and CRP) at wave 2 and mediated by nutrition and social isolation at wave 6 (Model 2), β coefficients (SE). Highlighted path lines represent significant associations

Table 8.6 SEM output of the age- and sex-adjusted association between edentulism at wave 3 and cognitive impairment at wave 8 preceded by inflammatory markers (fibrinogen and CRP) and mediated by inflammation, social isolation and nutrition at wave 6 (Model 2), β(SE) (n= 3,856)

	β (SE)	***p*-value**
Direct effects		
Fibrinogen → Edentulism	0.06 (0.07)	0.423
CRP[1] → Edentulism	0.05 (0.02)	0.005
Edentulism → Social isolation	0.19 (0.04)	<0.001
Fibrinogen → Social isolation	0.10 (0.06)	0.074
CRP → Social isolation	0.01 (0.02)	0.426
Edentulism → Nutrition	-0.17 (0.08)	0.023
Fibrinogen → Nutrition	-0.15 (0.10)	0.131
CRP → Nutrition	-0.04 (0.03)	0.125
Edentulism → Cognitive impairment	0.21 (0.06)	0.001
Social isolation → Cognitive impairment	0.11 (0.06)	0.077
Nutrition → Cognitive impairment	0.03 (0.02)	0.072
Fibrinogen → Cognitive impairment	0.12 (0.07)	0.103
CRP → Cognitive impairment	-0.02 (0.02)	0.229
Age → Cognitive impairment	0.05 (0.01)	<0.001
Sex → Cognitive impairment	-0.17 (0.08)	0.028
Intercepts		
Social isolation	0.99 (0.33)	0.003
Nutrition	5.32 (0.51)	<0.001
Indirect effects		
Fibrinogen → Edentulism → nutrition	-0.01(0.01)	0.449
CRP → Edentulism → nutrition	-0.01(0.01)	0.080
Fibrinogen→ Edentulism → Social isolation	0.01 (0.01)	0.428
CRP → Edentulism →Social isolation	0.01 (0.004)	0.018
Edentulism to cognitive impairment		
Sum of indirect effect	0.02 (0.01)	0.226
Edentulism → social isolation → cognitive impairment	0.02 (0.01)	0.098
Edentulism → nutrition → cognitive impairment	-0.01(0.004)	0.190
Fibrinogen to cognitive impairment		
Sum of indirect effect	0.01 (0.02)	0.433
Fibrinogen → Edentulism → social isolation → cognitive impairment	0.001 (0.002)	0.473
Fibrinogen → Edentulism → nutrition → cognitive impairment	<0.001(<0.001)	0.491
Fibrinogen → Edentulism → cognitive impairment	0.01 (0.02)	0.436
CRP to cognitive impairment		
Sum of indirect effect	0.01 (0.01)	0.023
CRP → edentulism → social isolation → cognitive impairment	0.001 (0.001)	0.155
CRP → edentulism → nutrition → cognitive impairment	<0.001 (<0.001)	0.234
CRP → edentulism → cognitive impairment	0.01 (0.01)	0.032
Measuring Model Fit		
CFI[2]	0.916	
TLI[3]	0.628	
RMSEA[4]	0.048	
SRMR[5]	0.138	

[1] C- reactive Protein
[2] Comparative Fit Index
[3] Tucker-Lewis Index
[4] Root Mean Square Error of Approximation
[5] Standardized Root Mean Square Residual

Summary

The sum of the indirect effects from oral health to cognitive impairment through all pathways: inflammatory, social and nutritional was stronger for edentulism and remained significant even after adjusting for age and sex. On the other hand, the sum of indirect effects for oral impacts was weaker and became non-significant after adjusting for age and sex. The only significant specific indirect pathway was the one from edentulism to cognitive impairment through social isolation. That association remained significant even after age and sex were included in the model. Although the indirect effects through nutrition were non-significant, the negative pattern was kept across all models. The indirect pathway through nutrition was close to significance level in the unadjusted model of the association between edentulism and cognitive impairment. However, the effect became non-significant after age and sex adjustment. On the other hand, the inflammatory markers, CRP in particular, were shown to be a significant precursor in the association between edentulism and cognitive impairment even after age and sex adjustment.

DISCUSSION

9 DISCUSSION

The overall aim of this thesis was to investigate the associations between poor oral health and the lower cognitive function as well as cognitive impairment in older adults. Cross-sectional and longitudinal data from a population study of older adults living in England (ELSA) were analysed to address the specific research questions proposed in Chapter 2.

Figure 9.2 summarises the suggested conceptual framework supporting the work included in this thesis about the potential associations between various indicators of oral health and cognitive impairment. This framework was represented as a cycle for two main reasons. The first is that the bidirectional association cannot be ruled out. The second reason is that it is an ongoing and continuous process of biological and lifestyle changes that impact oral and cognitive health throughout life.

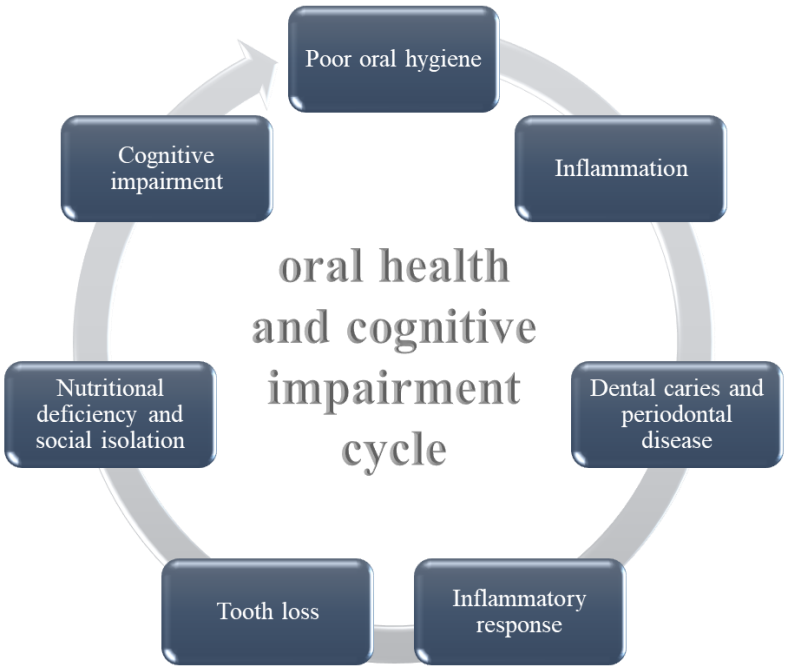

Figure 9.1 Oral health and cognitive impairment cycle

The findings from these analyses will be summarised and compared to other studies on oral health and cognition. The relevance of the findings will be then discussed in relation to causal pathways, followed by the strengths and limitations of the study. The relevance of the findings for policy and practitioners will be highlighted before the conclusion.

9.1 Oral health and cognition

9.1.1 Oral health and cognitive function

The first and second objectives of this thesis were to investigate the cross-sectional and longitudinal association between oral health at baseline (wave 3) and cognitive function, memory and executive function, at wave 3 for the cross-sectional study and wave 8 for the longitudinal study. The findings in Chapters 4 and 5 presented the cross-sectional and longitudinal associations for the overall sample first, and then for dentate and edentate participants separately (where appropriate). Table 9.1 includes the estimates of the associations of the full models in the cross-sectional and longitudinal analyses.

In the whole sample, edentulism was a strong predictor of lower cognitive function for cross-sectional and longitudinal analyses and for both cognitive domains; and the size of the statistically significant associations in the fully adjusted models varied from -0.48 (95% CI: -0.81, -0.15) to -1.01 (95% CI: -1.75, -0.27) (Table 9.1). On the other hand, poor self-reported oral health significantly predicted lower executive function in the cross-sectional analysis. Stratifying the sample, according to edentulism, substantially strengthened the associations between self-reported oral health and cognitive function in the edentate sample. For edentate participants, the estimates were significant with memory across all studies.

Furthermore, the associations between oral impacts and cognitive function for the overall sample, cross-sectionally and longitudinally, were non-significant. The associations were considerably stronger for the edentate sample but remained non-significant. Although oral impacts did not show any significant estimates, the results among the edentate sample in the longitudinal analyses showed the highest effect across all findings and varied from -2.13 (95% CI: -4.56, 0.29) in the time-lag analysis to -2.27 (95% CI: -4.65, 0.10) in the autoregressive model. This could be due to the lack of power because of the small sample for those who were edentate and reported oral impacts. Therefore, the 95% CI were wide and the results non-significant despite the magnitude of the actual estimate.

The results of the present study were in broad agreement with previous studies. The literature review in Chapter 2 identified 9 studies which assessed the association between oral health and cognitive function (Starr et al., 2008; Kamer et al., 2012; Stewart et al., 2008; Bergdahl et al., 2007; Naorungroj et al., 2013a;

Hansson et al., 2013; Ki et al., 2019; Matthews et al., 2011; Iwasaki et al., 2016; Del Brutto et al., 2014). All were cross-sectional designs, 4 of the studies used global cognitive tests, mostly the Mini-Mental State Examination (MMSE) (Starr et al., 2008; Bergdahl et al., 2007; Ki et al., 2019; Iwasaki et al., 2016). The rest of the studies used a single measure for each specific cognitive domain; mostly, the word recall test for memory (Stewart et al., 2008; Matthews et al., 2011; Naorungroj et al., 2013a). Tooth loss was included as an oral health indicator in most of the studies. Self-reported oral health was used in only one study (Del Brutto et al., 2014), while no previous study used a measure of oral impacts. This thesis found that age and education were the most critical covariates in the association between oral health and cognitive function. However, after stratifying the sample to dentate and edentate participants, the effect of age was reduced. The effect of age and education in the association between oral health and cognitive function is consistent with other studies (Bergdahl et al., 2007; Starr et al., 2008; Stewart et al., 2008; Matthews et al., 2011). Moreover, edentulism was found in this thesis to be positively associated with cognitive function, which is also consistent with other studies (Bergdahl et al., 2007; Naorungroj et al., 2013a).

Edentate participants in ELSA were found to be older (10 years older), non-cohabiting, lower education, poorer and had higher depressive symptoms. Hence, stratifying the sample into dentate and edentate showed stronger estimates for self-reported oral health and oral impacts predicting lower cognitive function among edentate participants. The estimates in the overall sample were highly influenced by the high prevalence of dentate participants in ELSA dataset. Edentulism is a crude and irreversible measure of oral health, representing total tooth mortality and reflecting the accumulation of oral disease throughout the life course. Therefore, it is probable that a large proportion of edentate participants at baseline had been edentate for a number of years. As follow-up measurements of the cognitive function outcomes extended 10 years past the ELSA baseline (ELSA Wave 8 data collected in 2016/17), it is assumed that being edentulous at some point in adulthood may be a potential signal of lower cognitive function later in life.

Table 9.1 Summary of the associations between oral health and cognitive function in the cross-sectional and longitudinal analyses: adjusted for demographic factors, socioeconomic factors, lifestyle behaviours and depressive symptoms, β (95%CI)

Outcome	**Memory**			**Executive function**		
Type of study (type of analysis)	**Cross-sectional[1] (linear regression)**	**Longitudinal (Time-lag)[2]**	**Longitudinal (autoregressive)[3]**	**Cross-sectional[1] (linear regression)**	**Longitudinal (Time-lag)[2]**	**Longitudinal (autoregressive)[3]**
Overall sample						
Self-reported oral health						
Excellent (ref)						
Good	-0.08 (-0.23, 0.07)	-0.12 (-0.33, 0.10)	-0.14 (-0.34, 0.06)	-0.21 (-0.50, 0.09)	-0.02 (-0.46, 0.43)	0.06 (-0.34, 0.46)
Poor	-0.11 (-0.30, 0.08)	-0.03 (-0.32, 0.26)	-0.04 (-0.31, 0.23)	**-0.58** (-0.96, -0.20)**	0.23 (-0.37, 0.82)	0.42 (-0.11, 0.95)
Edentulism						
Dentate (ref)						
Edentate	**-0.57*** (-0.77, -0.37)**	**-0.60** (-0.96, -0.24)**	**-0.48** (-0.81, -0.15)**	**-0.92*** (-1.31, -0.53)**	**-1.01**(-1.75, -0.27)**	**-0.95** (-1.61, -0.28)**
Oral impacts						
No impact (ref)						
At least one impact	-0.05 (-0.30, 0.20)	-0.22 (-0.60, 0.16)	-0.24 (-0.59, 0.11)	-0.42 (-0.91, 0.06)	-0.20 (-0.98, 0.58)	-0.09 (-0.79, 0.61)
Dentate sample						
Self-reported oral health						
Excellent (ref)						
Good	-0.04 (-0.20,0.12)	-0.05 (-0.27, 0.18)	-0.08 (-0.29, 0.13)	-0.10 (-0.43,0.22)	-0.02 (-0.48, 0.44)	0.04 (-0.36, 0.45)
Poor	-0.13 (-0.34,0.08)	0.01 (-0.30, 0.30)	-0.01 (-0.29, 0.26)	**-0.57** (-0.99, -0.15)**	0.30 (-0.31, 0.91)	0.49 (-0.05, 1.03)
Oral impacts						
No impact (ref)						
At least one impact	0.01 (-0.26,0.29)	-0.13 (-0.54, 0.27)	-0.2 (-0.57, 0.17)	-0.38 (-0.93,0.18)	0.19 (-0.63, 1.02)	0.33 (-0.40, 1.07)
Edentate sample						
Self-reported oral health						
Excellent (ref)						
Good	-0.30 (-0.67,0.08)	**-1.04**(-1.83, -0.25)**	**-0.92* (-1.65, -0.19)**	**-0.76* (-1.39, -0.14)**	0.38 (-1.35, 2.11)	0.50 (-1.21, 2.20)
Poor	**-0.61*(-1.13, -0.08)**	-0.92 (-2.07, 0.22)	-0.76 (-1.82, 0.30)	**-1.55***(-2.42, -0.68)**	-0.90 (-3.42, 1.62)	-0.70 (-3.17, 1.78)
Oral impacts						
No oral impact (ref)						
At least one impact	-0.39 (-0.95,0.17)	-0.75 (-1.87, 0.36)	-0.46 (-1.50, 0.57)	-0.66 (-1.59,0.27)	-2.13 (-4.56, 0.29)	-2.27 (-4.65, 0.10)

[1] Exposure was oral health and outcome was cognitive function both at wave 3. Model adjusted for demographic factors, socioeconomic factors, lifestyle behaviours and depressive symptoms at wave 3.
[2] Exposure was oral health at baseline (wave 3) and outcome was cognitive function at wave 8. Model adjusted for demographic factors, socioeconomic factors, lifestyle behaviours at baseline and depressive symptoms at follow-up (wave 8).
[3] Same adjustment for time-lag and additionally adjusted for the baseline outcome (cognitive function at wave 3).
p-value *<0.05, ** <0.01, ***<0.001

9.1.2 Oral health and the change in cognitive function

The previous section discussed the results of the cognitive function outcome, which was measured either cross-sectionally at wave 3 or longitudinally at wave 8. However, oral health was also hypothesised to have an impact on the change in cognitive function over time. Therefore, the effect of oral health on the change in cognitive function (memory and executive function) was examined in Chapter 6. Table 9.2 summarises the estimates of the associations of the associations between oral health and the rate of change in cognitive function from different mixed-effects models. For the change in memory, self-reported oral health did not show any significant results. Demographic factors, and age in particular, had a considerable effect on the association between edentulism and memory change.

On the other hand, oral impacts were a significant predictor of memory decline over time after adjusting for several covariates, although the association was marginally non-significant in the fully adjusted model. For the change in executive function, self-reported oral health and oral impacts did not show any significant results. While edentulism showed significant estimates predicting a change in executive function; although adjusting for socioeconomic factors, education in particular, resulted in a non-significant estimate.

The previous studies showed mixed and inconclusive results regarding the association between oral health and the change in cognitive function over time. Not all studies reported the results for specific cognitive domains, such as memory and executive function, but in fact, the majority of studies looked at overall cognitive change using global cognitive tests such as the MMSE or a modification of it (Iwasaki et al., 2019; Li et al., 2017; Stewart et al., 2013; Reyes-Ortiz et al., 2013; Batty et al., 2013; Kaye et al., 2010; Iwasaki et al., 2016). In a male sample only, Kaye et al. (2010) showed that for each tooth lost per decade, the risk of low cognitive test score increased from 9%-12%. Another study showed that having fewer teeth (0-12) was a significant indicator of a greater decline in total MMSE scores over a five-year follow-up (Reyes-Ortiz et al., 2013). In another study that was conducted on diabetic participants only, it showed that being edentate or having few teeth was significantly associated with a higher risk of having a low cognitive function (Batty et al., 2013).

Moreover, two Japanese studies showed that severe periodontal disease was significantly associated with faster cognitive decline (Iwasaki et al., 2016; Iwasaki et al., 2019). Another study from a Chinese older population, Li et al. (2017) revealed that having more teeth among older participants was significantly associated with a slower pace of cognitive decline. Another recent Chinese study, Petrovsky et al. (2019) showed that tooth symptoms were significantly associated with a faster rate of cognitive decline. On the other hand, few studies reported the impact of oral health on the change in specific cognitive domains such as memory or executive function (Stein et al., 2010b; Naorungroj et al., 2015; Tsakos et al., 2015). The Stein et al. (2010b) study was only on female participants and reported that persons with less than 9 teeth at baseline had faster memory decline measured by the delayed word recall test. Another study in the US reported a similar measure that used in this thesis, the delayed recall test, and it showed that edentulousness did not significantly predict memory decline (Naorungroj et al., 2015). Moreover, Tsakos et al. (2015), who also assessed the impact of edentulism on memory change using ELSA dataset, reported similar findings to what was reported in this thesis. It showed that socioeconomic status played a significant role in explaining the association between oral health and changes in memory over time.

Contrary to what was presented in the previous section with cognitive function, oral impacts showed a stronger impact on the change in memory function compared to edentulism. Oral impacts including poor eating function, difficulties with speaking and communication and emotional problems may lead to lower self-esteem and reduced self-confidence (Davis et al., 2000) This reduction in confidence is expected to increase the chances of loneliness and social isolation (Rouxel et al., 2017b) which might lead to accelerating cognitive decline. The same effect was not observed with the change in executive function.

Table 9.2 Summary of the associations between oral health and the change in cognitive function across different adjusted model, β (95%CI)

	Model 1		Model 2		Model 3		Model 4		Model 5	
Outcome: Memory change										
Self-reported oral health										
Good oral health	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.01)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)
Poor oral health	0.02	(-0.03, 0.07)	-0.01	(-0.05, 0.04)	0.01	(-0.05, 0.05)	0.01	(-0.05, 0.05)	0.01	(-0.04, 0.06)
Edentulism										
Edentate	**-0.19*****	**(-0.25, -0.14)**	-0.04	(-0.10, 0.01)	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)
Oral impacts										
At least one impact	**-0.10****	**(-0.17, -0.04)**	**-0.08****	**(-0.14, -0.02)**	**-0.07***	**(-0.13, -0.01)**	**-0.07***	**(-0.13, -0.01)**	-0.06	(-0.12, 0.00)
Outcome: Executive function change										
Self-reported oral health										
Good oral health	-0.01	(-0.08, 0.07)	-0.01	(-0.09, 0.06)	-0.01	(-0.08, 0.07)	-0.01	(-0.08, 0.07)	-0.01	(-0.08, 0.07)
Poor oral health	0.08	(-0.02, 0.18)	0.04	(-0.05, 0.14)	0.06	(-0.04, 0.16)	0.06	(-0.04, 0.16)	0.07	(-0.03, 0.17)
Edentulism										
Edentate	**-0.31*****	**(-0.42, -0.21)**	**-0.12***	**(-0.23, -0.01)**	-0.10	(-0.21, 0.01)	-0.10	(-0.21, 0.01)	-0.10	(-0.21, 0.01)
Oral impacts										
At least one impact	-0.06	(-0.18, 0.07)	-0.03	(-0.16, 0.09)	-0.01	(-0.14, 0.11)	-0.01	(-0.13, 0.11)	0.01	(-0.12, 0.13)

Model 1: Adjusted for oral measure (self-reported oral health/edentulism/oral impact) + time and interaction of time with oral measure
Model 2: Adjusted for model 1 + age, sex, marital status and the interactions of time with age, sex, marital status
Model 3: Adjusted for model 2 + education, wealth and the interactions of time with education and wealth
Model 4: Adjusted for model 3 + smoking, alcohol and the interactions of time with smoking and alcohol
Model 5: Adjusted for model 4 + depressive symptoms and the interaction of time with depressive symptoms
p-value *<0.05, ** <0.01, ***<0.001

9.1.3 Oral health and cognitive impairment

In the overall sample, edentulism and oral impacts significantly predicted the subsequent cognitive impairment after adjusting for demographic and socioeconomic factors, lifestyle behaviours and depressive symptoms. The odds of having cognitive impairment for edentate participants and those who reported at least one oral impact ranged between 1.49 to 1.53 in the fully adjusted model. Table 9.3 summarises the estimate of the associations between oral health and cognitive impairment. Self-reported oral health did not show any significant estimates predicting cognitive impairment. Stratifying the sample into dentate and edentate participants showed stronger results among dentate participants and no significant findings among edentate participants.

As described in the literature review, 17 studies reported the findings of the associations between oral health to cognitive impairment, 6 longitudinal and 11 cross-sectional in nature. Assessment of cognitive impairment was based either on medical records (Shimazaki et al., 2001) or by a specialist diagnosis, a neurologist or a psychologist, (Gil-Montoya et al., 2015b; Luo et al., 2015; Okamoto et al., 2017; Iwasaki et al., 2019) or by a validated definition using a predetermined cut-off point of a global cognitive test, mostly the MMSE, (Stewart and Hirani, 2007; Okamoto et al., 2010; Lexomboon et al., 2012; Park et al., 2013; Saito et al., 2013; Stewart et al., 2013; Nilsson et al., 2014; Wang et al., 2014; Iwasaki et al., 2015; Okamoto et al., 2015; Peres et al., 2015; Kim et al., 2017). Most of the studies used the number of teeth, either self-reported or clinically measured, as the indicator of oral health. None of the identified studies used oral impacts as a potential predictor of cognitive impairment.

The findings of this thesis were in agreement with many studies which indicated that either being edentate or having a fewer number of teeth was significantly associated with cognitive impairment adjusting for a variety of covariates. Some studies showed mixed results such as Nilsson et al. (2014) which showed significant results for edentulism but non-significant results for having fewer teeth. Another study showed a strong association between edentulism and impaired cognition in a community sample but no significant association among those who lived in care homes (Stewart and Hirani, 2007). In a Japanese longitudinal study over 5-years, Okamoto et al. (2015) showed that being edentate or having few teeth was significantly associated with higher odds of cognitive impairment. A

previous clinical study showed an aggravated systemic inflammation in subjects who had both conditions, periodontal disease and cognitive impairment. This suggests a higher risk of advancing to dementia with an elevated level of oral inflammation (Sochocka et al., 2017). Additionally, a recent 5-year longitudinal study showed that participants with severe periodontal inflammation had significantly higher odds of having mild cognitive impairment than those without (Iwasaki et al., 2019). On the other hand, multiple studies showed no significant results between oral health and cognitive impairment (Shimazaki et al., 2001; Lexomboon et al., 2012; Stewart et al., 2013; Wang et al., 2014; Gil-Montoya et al., 2015b; Luo et al., 2015; Kim et al., 2017).

Those who suffer from fast cognitive decline are at higher risk of being affected with cognitive impairment (Ray and Davidson, 2014). Therefore, this thesis also investigated how oral health could predict cognitive impairment after presenting the findings with the change in cognitive function. The results of the whole sample showed almost equal and higher odds of cognitive impairment for those who were edentate (compared to dentate) and those who reported at least one oral impacts (compared to those who did not experience oral impacts). However, after stratifying the sample into dentate and edentate, the significant effect of oral impacts on cognitive impairment was sustained only among the dentate sample. The negative results from the edentate sample could be due to the small edentate sample, which compromised the power to detect the significant difference. Some of the subgroups were very small; for example, participants who were edentate and cognitively impaired (n=10) and those who reported poor oral health and were cognitively impaired (n= 11).

Table 9.3 Summary of the associations between oral health and the subsequent cognitive impairment, OR (95% CI).

Outcome: cognitive impairment	**OR (95% CI)[1]**
Overall sample	
Self-reported oral health	
Excellent (ref)	
Good	1.04 (0.79, 1.36)
Poor	0.86 (0.60, 1.25)
Edentulism	
Dentate (ref)	
Edentate	**1.53** (1.11, 2.12)**
Oral impacts	
No impact (ref)	
At least one impact	**1.49* (1.01, 2.21)**
Dentate sample	
Self-reported oral health	
Excellent (ref)	
Good	1.14 (0.84, 1.54)
Poor	0.86 (0.57, 1.30)
Oral impacts	
No impact (ref)	
At least one impact	**1.58* (1.00, 2.47)**
Edentate sample	
Self-reported oral health	
Excellent (ref)	
Good	0.84 (0.45, 1.57)
Poor	1.38 (0.57, 3.34)
Oral impacts	
No impact (ref)	
At least one impact	1.11 (0.48, 2.58)

[1]Adjusted for demographic and socioeconomic factors, lifestyle behaviours and depressive symptoms

9.1.4 The pathways of the association between oral health and cognitive impairment

One of the major strengths of this study was to investigate the mechanism or pathways of the association between oral health and cognitive impairment. The pathways explored were not restricted to the association from oral health to cognitive impairment only, but also included the role of inflammation as a precursor to edentulism before it leads to cognitive impairment. Three main pathways were examined: inflammatory, nutritional and social pathways. Inflammatory and nutritional pathways were suggested in the previous literature (Wu et al., 2016; Noble et al., 2013), but the social pathway has not been previously identified as a potential pathway in the association between oral health and cognitive impairment. Table 9.4 highlights the main findings of several SEMs of different potential pathways. For the first pathway, 0.04 of the effect of edentulism on the subsequent cognitive impairment was explained by the indirect effect of social isolation (SE= 0.02, p-value =0.049) adjusted for age and sex. The same effect was not observed in the pathway from the oral impact to cognitive impairment. The third and fourth pathways explored the association between edentulism and cognitive impairment preceded by inflammatory markers (CRP and fibrinogen). The analysis showed a significant 0.01 indirect effect of the edentulism in the association between CRP inflammatory marker and cognitive impairment (SE= 0.01, p-value =0.032).

Different pathways were suggested in the previous literature linking oral health to cognitive impairment; although there were no studies empirically assessed or investigated these pathways. The common inflammatory pathway was mostly suggested in studies which included periodontal disease as a potential predictor of cognitive impairment (Nascimento et al., 2019). Patients diagnosed with periodontitis present higher levels of inflammatory mediators such as serum CRP (Ardila and Guzman, 2015) and it has been suggested that the periodontal infection and the inflammatory response against periodontal pathogens may increase the susceptibility to impaired cognition (Pazos et al., 2018). Another study highlighted that periodontal disease might not initiate cognitive impairment but exacerbate the systemic inflammation which in turn accelerates the neurodegenerative process (Sochocka et al., 2017). This thesis did not show any significant indirect effect of inflammation in the association between oral health and cognitive impairment; although there was no information about the current periodontal status of the

respondents in ELSA. Edentulism in this thesis was assumed to be the crude measure of previous accumulation of oral diseases, including periodontal inflammation. Therefore, the finding of this thesis confirmed the CRP inflammatory marker to act as a precursor to edentulism in the association with cognitive impairment. The second pathway was a nutritional deficiency. Many studies discussed the effect of tooth loss on chewing and mastication function; and how that could lead to cognitive impairment (Weijenberg et al., 2019; Okamoto et al., 2017; Kim et al., 2017; van de Rest et al., 2015; Elsig et al., 2015; Meeusen, 2014). ELSA dataset did not have full nutrition assessment tool; instead, this thesis used the average fruit and vegetable portions consumed every day. This could explain the null findings in this thesis when nutrition deficiency was examined as a potential pathway.

Finally, the social pathway has never been identified as a potential pathway. However, social isolation, in particular, was listed as one of the most important modifiable risk factors to prevent dementia among the older population (Livingston et al., 2017a). Hence, this thesis examined the role of social isolation, as a result of poor oral health, on cognitive impairment. The results showed a positive association confirming the indirect effect of social isolation in the association between edentulism and cognitive impairment. Since there were no previous studies that looked at the effect of social isolation mediating the association between oral health and cognitive impairment, the findings of this thesis cannot be compared to others. However, it should be noted that social isolation was significantly reported as a mediator in the association between walking and loneliness among the elderly (Shellito and Roldan, 2019). The study reported that a positive association between social isolation and loneliness. Another study used the same dataset used in the thesis, ELSA dataset and it showed that older people who experience high levels of social isolation are at increased risk of becoming physically frail. Therefore, the findings of this thesis are consistent with other studies reported the impact of social isolation on loneliness and frailty. Social isolation in this thesis acted as a significant indirect effect in the association between edentulism and cognitive impairment.

Table 9.4 Summary of the indirect effects of different mediators in the associations between oral health and cognitive impairment, β (SE).

Pathway	β (SE)[1]	p-value
Edentulism to cognitive impairment		
Sum of indirect effect	**0.04 (0.02)**	**0.043**
Edentulism → nutrition → cognitive impairment	-0.01(0.01)	0.278
Edentulism → social isolation → cognitive impairment	**0.04 (0.02)**	**0.049**
Edentulism → inflammation → cognitive impairment	0.02 (0.01)	0.152
Oral impacts to cognitive impairment		
Sum of indirect effect	0.03 (0.02)	0.089
Oral impacts → nutrition → cognitive impairment	-0.002 (0.003)	0.511
Oral impacts → social isolation → cognitive impairment	0.02 (0.01)	0.196
Oral impacts → inflammation → cognitive impairment	0.01 (0.01)	0.212
Fibrinogen to cognitive impairment		
Sum of indirect effect	0.01 (0.02)	0.433
Fibrinogen → edentulism → social isolation → cognitive impairment	0.001 (0.002)	0.473
Fibrinogen → edentulism → nutrition → cognitive impairment	<0.001(<0.001)	0.491
Fibrinogen → edentulism → cognitive impairment	0.01 (0.02)	0.436
CRP to cognitive impairment		
Sum of indirect effect	0.01 (0.01)	0.023
CRP → edentulism → social isolation → cognitive impairment	0.001 (0.001)	0.155
CRP → edentulism → nutrition → cognitive impairment	<0.001 (<0.001)	0.234
CRP → edentulism → cognitive impairment	**0.01 (0.01)**	**0.032**

[1] SEM models adjusted for age and sex

9.2 Strengths and limitations of the study

9.2.1 Strengths

9.2.1.1 Study setting and quality of data

This thesis investigated the research question using different samples extracted from the ELSA dataset. The dataset was obtained from a large representative national sample of older adults, aged 50 years and older, living in England. It included information about oral health, general health, cognitive function and a wide variety of potential confounders and mediators of the association between oral health and cognition. The literature review concluded that few studies of oral health and cognition were from large and representative population-based samples.

9.2.1.2 Longitudinal data

The strengths of this thesis derive primarily from the use of the ELSA data to examine whether oral health is a predictor of cognitive function among older adults. This enabled the use of longitudinal data to analyse the effect of oral health on the change in cognitive function among older adults. The strengths of such longitudinal data to enable stronger inference in relation to the key research question of the thesis have already been discussed above.

9.2.1.3 Length of follow-up

The analysis of this thesis included data from wave 2 (2004-05), where inflammatory markers included in the SEM as a precursor to edentulism (Chapter 8); the baseline oral health data obtained from wave 3 (2006-07) and the follow-up cognitive outcomes data from waves 3 to 8 (2006-07-2016-17). Hence, this project used data that been collected over a 12-years and used the latest available ELSA dataset. Very few studies in the literature that reported the effect of oral health on cognitive impairment with sufficient time to detect the impact.

9.2.1.4 Diversity of cognitive domains

This thesis assessed cognition in different ways. In Chapters 4 and 5, cognition was assessed as a continuous score in cross-sectional and longitudinal fashion to explore the association between oral health and cognitive function. Then, in Chapter 6, the change in cognitive function was assessed to investigate whether

oral health was associated with faster or slower decline in memory and executive function. The following chapters, Chapter 7 and 8, utilised a widely used global cognitive test, The Modified Telephone Interview for Cognitive Status (mTICS), to assess the association between oral health and cognitive impairment. The goal was to assess the impact of oral health on cognition in different steps; whether poor oral health was associated with lower cognitive function or faster cognitive decline or higher odds of cognitive impairment.

9.2.1.5 Diversity of oral health measures

Oral health measures were analysed in this thesis to reflect different aspects of current and historical oral health. These include self-reported oral health which evaluates the current perception of oral health condition. Edentulism is a crude and broad oral health measure that reflects the accumulation of oral disease over the life course and the experience of dental treatment. It is an irreversible condition which makes it a robust measure of total tooth mortality (Tsakos, 2011). Oral impacts capture the overall oral health, which in turn is related to the quality of life, a multidimensional concept that incorporates oral health morbidity, disability and impairment, social, psychological and physical functioning. Furthermore, this measure has been validated for use among English older adults (Tsakos et al., 2011). This incorporates a broader multidimensional subjective assessment of oral health, rather than just clinical morbidity (Locker et al., 2005).

9.2.1.6 Controlling for relevant confounders

Another strength of the thesis is the range of potential confounders that were controlled for in the longitudinal analysis and the analysis of change. The ELSA dataset contains detailed measures of potential confounders of the association between oral health and cognitive function among older adults. For example, this thesis used household wealth as one of the measures of socioeconomic position. Wealth is a better measure of the long-term economic status of older people compared to income (Demakakos et al., 2016).

9.2.1.7 Using inflammatory biomarkers

To assess inflammation as a potential mediator or a precursor in the association between oral health and cognitive impairment, inflammatory markers, WBC, CRP and fibrinogen were obtained from ELSA respondents. These inflammatory

markers were used to create a latent variable for inflammation which was used in the SEM models assessing the role of inflammation as an influential factor.

9.2.1.8 Pathways analysis

This thesis explored the role of different pathways in the association between oral health and cognitive impairment. Using a variety of ELSA waves allowed the potential pathways to be examined, maintaining the chronological order of exposure, mediators and outcome. Additionally, ELSA dataset is very rich in social covariates which allowed the social pathway to be tested and examined for the first time; to the best of our knowledge.

9.2.2 Limitations

9.2.2.1 Missing data

From the total eligible baseline sample 7,924, there was almost 38% missingness due to attrition; 12% were known to be dead, 10% were alive but did not participate, and 16% had no information about their living status. A further 11% of respondents had missing data on cognitive measures, and 3% had missing data on depressive symptoms. Hence, the analysis may be biased because the ELSA respondents who were older, poorer and had poorer health were more likely to be missing. As the lower socioeconomic status and poorer health was associated with lower cognitive function and poorer oral health, the direction of bias suggests that the reported associations between oral health and cognitive function would possibly be stronger if this group of missing respondents in the baseline sample were included. This suggests that the data are not missing completely at random. Further imputation analysis assuming missing at random or missing not at random mechanisms was beyond the scope of this thesis.

9.2.2.2 Measures of oral health status

In this thesis, there is a risk of low specificity because oral health measures were self-reported only and there is no clinical data to confirm the findings. Additionally, the analysis of tooth loss employs a very crude measure of total tooth loss (presence or absence of edentulism) and does not allow for testing a more refined measure that would reflect extent of tooth loss. More detailed tooth loss data based on the number of teeth will give detailed information about the difference between functional and non-functional dentition in the association with cognitive impairment.

Also, the lack of periodontal measure in ELSA limited the analysis of the inflammatory pathway.

9.2.2.3 Cognitive impairment measure

Although the ELSA dataset is rich in cognitive measures, the Modified Telephone Interview for Cognitive Status (mTICS), a measure for cognitive impairment used in Chapter 7, was first collected at wave 7. Hence, analysing the autoregressive model to remove the cross-sectional part of the relationship in the longitudinal analysis between oral health at wave 3 and cognitive impairment at wave 8 was not possible. It should be noted that mTICS has not been used in previous studies that assessed the association between oral and cognitive impairment. Most of the studies used the Mini-Mental State Examination (MMSE) which is not available in the ELSA dataset. Therefore, comparing the findings, in this thesis, regarding the association with cognitive impairment was difficult.

9.3 Implications of the findings

9.3.1 Research implications

This thesis highlights the potential effect of oral health on cognition and confirms the importance of further research to investigate the different pathways that explain the association. The research should be extended to the effectiveness of restoring functional dentition on improving nutrition. Also, the effectiveness of reducing oral infection in cognitive health should be tested in well-constructed interventional studies.

Another key finding of this thesis was the importance of further assessment of the social pathway in maintaining cognitive health. Social engagement was identified as a modifiable risk factor to prevent the onset and progress of cognitive impairment. It is very important to identify the role of oral health in improving social life among older adults; and whether that improvement will influence cognitive health.

This thesis focused mainly on oral health as a predictor of cognitive health and impairment. However, the bidirectional association between oral health and cognitive impairment was suggested in the literature, and further research on the mechanism of pathways in the other direction is highly encouraged.

9.3.2 Policy implications

The knowledge about the association between oral health and cognitive impairment is important, as it opens new doors for preventive strategies to face the deterioration of cognitive function. Many non-modifiable risk factors associated with cognitive impairment, namely ageing and genetics cannot be altered. However, risk factors related to oral health are modifiable and might infuse new hope for preventive interventions.

Although not scientifically confirmed, the treatment of active oral inflammation, maintaining or restoring the aesthetic and masticatory function could help prevent or possibly delay the onset and progression of cognitive decline in the future. Taken together, our findings are consistent with the hypothesis that functional dentition help to maintain cognitive functioning. Hence, geriatric dentistry should be an area of health priority, especially given that many older adults have poor oral health. Additionally, oral health care should be emphasised and become a priority in nursing homes. Nutritionists should encourage elderly and their caretakers to have healthier diets for the elderly that improve oral health.

Finally, health authorities should improve funding and resources to prioritise the elderly for oral health promotion and screening programmes. The improved quality of life will significantly lower morbidity and mortality and lower care costs.

9.4 Conclusion

This thesis has examined whether oral health was a determinant of lower cognitive function, faster cognitive change, or having an impaired cognition among older adults in England. It showed clear evidence that edentulism can predict lower memory and executive function; while self-reported oral health showed weaker evidence predicting lower memory for those who were edentate. The thesis also showed weak evidence that oral impacts predicted memory decline, although this association was not significant after adjusting for depressive symptoms. Edentulism and oral impacts were strong predictors of subsequent cognitive impairment independent of many covariates. The association between edentulism and cognitive impairment was significantly mediated by social isolation and preceded by inflammation.

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APPENDICES

Appendix A List of studies of the association between oral health and cognitive functioning

(Appendix A) Study reference	Population and sample	Study design	Oral health Measures	Cognitive measure	Covariates	Statistical method	Main findings
Bergdahl et al., 2007 Sweden	211 dentate and 188 with comparable age and gender selected from test wave 1993-1995 Age: 50 years and older	cross-sectional part of a large-scale longitudinal population-based study (Betula study)	Self-reported: Natural teeth Dentate vs. edentate	12 different tests: MMSE, face recognition, recognition of action and sentences, recall of test session, recall focused/divided attention, prospective memory, word fluency, block design, tower of Hanoi	Age, gender, SES, social network, diseases(cardio-vascular disease, high blood pressure, blood disease, stroke, diabetes, neurological disease, psychiatric disease, head injury, encephalitis, back problem, tumour disease, thyroid disease, hormone disease, gastro-intestinal disease, gynaecological disease, skin disease, allergy, lung disease, eye disease, ear, nose, and throat disease, arthritis, bone fracture and infectious disease), stress	MANOVA and stepwise multiple regression analysis	Dentate had higher cognitive performance. The associations were weak and only to MMSE and 7 cognitive tests: Recognition sentences, Recall focused attention, Recall divided attention, Recall of test session, Prospective memory, Word fluency (Animals in 1 min), and Block design. Age and education accounted for most of the variance.
Starr et al., 2008 Edinburgh (Scotland)	201 Age: 70 years and older	cross-sectional Performed at the follow-up wave	Self-reported: Tooth loss Dentate vs. edentate	MMSE Verbal memory (the Logical Memory test)	Age , occupational class and IQ	General linear models	Being edentulous was associated with significantly lower mean scores on MMSE ($F = 7.85$, $p = 0.006$), and logic memory ($F = 6.00$, $p = 0.015$). Associations became non-significant once IQ and age were adjusted for.
Stewart et al., 2008 U.S. NHANES-III	Two samples: 5,138 aged 20-59 1,555 aged 70 and older	A secondary analysis	Clinical examination: (1)extent of gingival bleeding on probing (ratio of examined sites) (2) extent of loss of attachment 3 mm (proportion of examined sites) (3) number of missing tooth surfaces	(1) The Symbol Digit Substitution Test (SDST), and the Serial Digit Learning Test (SDLT) for group aged 20-59 (2) the Story Recall test for aged 70	Age, sex, years of education, ethnicity. Socioeconomic status was derived, using a poverty index calculated as the ratio of household income to the poverty threshold in the calendar year of interview. Ischemic heart disease, angina pectoris, heart attack, stroke; hypertension; diabetes; and smoking status. Physical activity	Linear regression	Tooth loss is a strong factor for the story recall test in the older sample, regression coefficient (95% CI) 0.006 (0.002–0.011) $p<0.05$ After adjusting for education, the regression coefficient for tooth loss and story recall 0.001 (0.003–0.005) and it was not significant

(Appendix A) Study reference	Population and sample	Study design	Oral health Measures	Cognitive measure	Covariates	Statistical method	Main findings
Grabe et al., 2009 Germany	1,336 Age: 60–79 years	Cross-sectional study	Clinical examination: Number of teeth	MMSE	Age, BMI, cardiovascular parameters and psychosocial parameters like school education, income, smoking and alcohol consumption	Tobit regression	Low number of teeth was significantly associated with lower MMSE among female only. The coefficient estimates (SE) in the fully adjusted model among female was 0.045 (0.017) 95% CI= 0.011–0.079.
Matthews et al., 2011 U.S. The REGARDS study	9,853 Age 45 and older	Cross-sectional study	Self-reported: Tooth loss “Have you lost any of your teeth owing to gum disease?” and “How many teeth have you lost owing to gum disease?” Answers categorized as 0, 1-5, 6-16 and >16 teeth lost	The Word List Learning (WLL): (Phone interview) (1) Learning score- the average of three trials to recall 10 words (0-10) (2) Delay recall score- the score of single try to recall words after 5 minutes (0-10)	Age, sex, region, race, BMI, logCRP, diabetes, hypertension, hyperlipidemia, smoking, CES-D, income, education	Incremental linear regression modelling	Tooth loss due to periodontitis was not associated independently with lower scores for learning and recall in the full models. SES (income and education) explained the association. Losing more than 16 teeth significantly associated with the mean learning score (ß [95% CI]) −0.16 (−0.29 to −0.04) but after adjusting for income and education, the association was not significant.
Naorungroj et al., 2013 U.S. The ARIC study	9,874 Age: 62.8 years on average African American and white participants who received a cognitive assessment and dental screening interview at visit 4 (1996-1998)	Cross-sectional study	Clinical examination: (1) complete tooth loss, (2) number of teeth, (3) periodontitis, (4) plaque deposits, (5) gingival inflammation, (6) oral hygiene care (7) dental utilization	(1) Delayed Word Recall (DWR) Test (2) Digit Symbol Substitution (DSS) Test (3) Word Fluency (WF) Test cognitive decline: race- and gender-specific ‘studentized’ residuals between examination 2 and 4	Age, sex, race/study centre, education, income, smoking, alcohol use and diabetes	Linear regression	Complete tooth loss was significantly associated with lower DWR (delayed word recall) , DSS (digit symbol substitution) and WF (word fluency) scores in the fully adjusted model. Regression coefficients for complete tooth loss were attenuated greatly after adjusted for sociodemographic factors. The number of teeth was no longer associated with DWR scores after we adjusted for sociodemographic factors. The adjusted associations with DSS (b = 0.069 per tooth, P = .0003) and WF (b = 0.086, P = .0002) were significant in the final models.

(Appendix A) Study reference	Population and sample	Study design	Oral health Measures	Cognitive measure	Covariates	Statistical method	Main findings
Hansson et al., 2013 Sweden	273 Age 55-80 years randomly selected from the fifth test wave (2008–2010) of the ongoing Betula Prospective Cohort Study on memory, health, and cognition	Cross-sectional study	Clinical examination: (1) number of teeth, (2) occlusion (3) periodontal conditions (4) caries (5) fillings (6) root fillings (7) prosthetic treatment	11 different tasks to assess several domains: 3 tasks for episodic memory, 2 tasks for semantic memory, 2 tasks for working memory, 3 task for processing speed and one task for visuospatial ability	Age, education, gender, occupation, and living condition	Hierarchical regression analysis	Number of natural teeth was positively associated with performance on episodic memory: recall (ß= 0.20; P < 0.002) as well as episodic memory: recognition (ß= 0.24; P < 0.002)
Del Brutto et al., 2014 Ecuador (rural)	274 participants Age: > 60 years	cross-sectional study	Clinical examination: (1) Tooth loss (Edentulism) (2) self-rated oral hygiene	MoCA	age, sex, years of education, CVH status, depression, and dementia	Linear regression	Significant lower MoCA scores for persons with <10 remaining teeth, (β=-1.06, p = 0.03). No cut-off point, MoCA used as continuous. Self-reported oral health was not significant.
Iwasaki et al., 2016 Japan	85 participants Age: >75 years	Longitudinal Follow up after 3 years	Clinical examination: Severe periodontitis vs no severe periodontitis	MMSE	age, gender, education, depression, BMI, smoking status, alcohol use, exercise, hypertension, diabetes, and history of CVD and stroke	Time-lag linear regression	severe periodontitis is significantly associated with future decline in cognitive function among community-dwelling older Japanese subjects. The estimates (ß=-1.8, 95% CI: -3.3 , -0.2) in the full model.
Ki et al., 2019 Korea	1115 participants Age: 70-84 years	Cross-sectional study	Radiographic examination: Tooth replacement either none, pontics only, pontics and implants, and implants only.	MMSE	age and sex, smoking, alcohol, BMI, hypertension, cerebrovascular disease, coronary artery disease, asthma or chronic obstructive pulmonary disease, osteoporosis, diabetes mellitus, depression, and other psychiatric disorders, hs-CRP, number of natural teeth, periodontitis , chewing discomfort, tooth-brushing frequency, education level, participation in economic activity, living alone, and marital status.	Multiple linear regression	The multiple adjusted model showed positive results for tooth replacement implant group only to be significantly associated with cognitive function (ß=0.85, SE: 0.40 , P-value = 0.034)

Appendix B List of studies of the association between oral health and the change of cognitive functioning

(Appendix B) Study reference	Population and sample	Study design	Oral health measures	Cognitive measures	Covariates	Statistical method	Main findings
Kaye et al., 2010 U.S.	Baseline: 1968 Original N = 1,231 97% white, 3% black Current study: n = 597 men Aged 24–84 community-dwellers Follow-up: up to 32 years (until 2002) Department of Veterans Affairs	Longitudinal study	Oral examination every 3 years (between 1968 &2002): (1) number of teeth (2) maximum probing pocket depth for each tooth (3) alveolar bone loss, (4) caries or restoration (~every 3 years) by calibrated periodontist	measured between 1993 and 2001: (1) MMSE (low score <25, or <90% of age- and education-specific median) (2) spatial copying task (SCT) low score <10	Age, education smoking, aspirin use, nonsteroidal anti-inflammatory drugs, BMI, coronary heart disease, stroke, hypertension, CVD, cancer, diabetes mellitus, alcohol, coffee, tea, folate, B6, B12	Risks of developing low MMSE or SCT scores in relation to tooth loss, progression of periodontal disease, and progression of caries were estimated using adjusted hazard ratios (HRs)	For each tooth lost/decade the risk of low cognitive test score increases from 9%-12%. For each tooth had progression of alveolar bone loss or periodontal probing the risk of low cognitive function increases from 2% to 5%
Stein et al., 2010 U.S.	Baseline: 1991–1992 N = 144 nuns Aged 75–98 n = 32 with dementia n = 112 without dementia n = 101 with adequate follow-up data Follow-up: annual, 12 years	Longitudinal study	Dental records (40 Ys): (1) Number of teeth excluding non-third molars present at first cognitive evaluation (2) Presence of periodontal damage	(1) Delayed word recall (Memory)	Age, education, APOE e4 status Medical history in dental records (n = 133) Medical conditions associated with inflammatory process	non-linear mixed-effects regression model. The random effects (within as well as between) were assumed to follow independent normal distribution with mean zero and unknown variance	Poorer DWR (memory) at baseline and faster cognitive decline among persons with APOEε4, ≤9 teeth, or both than those with one or neither risk factors

(Appendix B) Study reference	Population and sample	Study design	Oral health measures	Cognitive measures	Covariates	Statistical method	Main findings
Stewart et al., 2013 U.S.	Baseline: 1997/1998 N = 947 Age 70–79 M=~50%; F=~50% black 34%, white 66% Healthy Medicare community residents in local area, unimpaired basic ADL or mobility. Included all blacks, and random sample of whites Follow-up: Year 5 The Health, Aging and Body Composition study	Longitudinal study	Oral examination: (1) number of teeth (2) number of occluding pairs (3) mean probing depth (4) attachment loss (5) mean of gingival index (6) mean plaque score (7) number of bleeding sites on probing All measures categorized into quartiles for analysis	(1) Modified MMSE (3MS) Y1, Y3, Y5): Cognitive impairment defined as core <80 of 3MS (bottom 10%, based on average at Y1&Y3) Cognitive decline defined as drop of ≥5 points of 3MS (most declining 20%) (2) DSST at Y1, Y5 (3) clock drawing at Y3 Cognitive impairment for both: bottom 10%	Age, sex, education, race, BMI, cardiovascular disease and risk, and depressive symptoms using CES-D score, CRP, Interlukin-6 at Y1, Weight loss at Y1 to Y3, Anticholinergic medications, APOEε4	Cognitive impairment and cognitive decline were modelled as binary dependent variables with quartiled oral health measures as primary independent variables, the latter entered into logistic regression models as ordinal variables	For cognitive decline: No significant associations. Gingival inflammation was close to significance. For cognitive impairment: In the fully adjusted model, no significant association found between any dental measure and 3MS except for gingival inflammation (gingival index (GI) and plaque index (PI) scores). The OR (95% CI) for the mean GI at Y2 with cognitive impairment (from average 3MS from Y1&Y3) was 1.55 (1.17–2.06) and for the PI was 1.34 (1.05–1.72)
Reyes-Ortiz et al., 2013 U.S.	Wave 1: 1993-1994, n= 3,032 Wave 2: 1995-1996, n= 2,424 Wave 3: 1998-1999, n= 1,967 Baseline (Wave 1) and at follow-up (Waves 2 and 3) Age 65 and older Mexican Americans Follow-up: 5 years The Hispanic Established Populations for Epidemiologic Studies of the Elderly (EPESE)	Longitudinal study.	Self-reported: Number of teeth: 1) 0 (or none, edentulous); 2) 1-12 (or ¼); 3) 13-19 (or ½); 4) 20-27 (or ¾); and, 5) 28-32 (or all) Then a dichotomized variable created as less than half (0-12) vs. half or more (13-32)	(1) total MMSE scores (0-30) (2) memory domain (0-6) (3) no-memory domain (0-24)	socio-demographic characteristics, last dental office visit, medical conditions, depressive symptoms, and functional limitations	Multivariate longitudinal analyses (MIXED procedure) for each MMSE global domain (memory; no-memory) and total MMSE score as a function of the number of teeth (dichotomized). A cross-sectional analyses (without the number of teeth/time interaction term) and longitudinal analyses (with the number of teeth/time interaction term)	For the longitudinal results, those with fewer teeth (0-12) compared to participants with more teeth (13-32), had a greater decline in total MMSE scores through five years of follow-up. There was a drop of 0.12 fewer points each year in the fully adjusted model (SE ± 0.05, p <0.01).

(Appendix B) Study reference	Population and sample	Study design	Oral health measures	Cognitive measures	Covariates	Statistical method	Main findings
Batty et al., 2013 Europe	Baseline: 2001–2003 N = 11,140 M = 6,407; F = 4,733 Aged 55–88 (all with type II diabetes mellitus and history of major macro- or microvascular disease or ≥1 other cardiovascular risk factor) White (67%) (other ethnicities not reported) Follow-up: 5 years ADVANCE trial	Longitudinal study	self-reported: (1)number of natural teeth connected to gum or jawbone (2) number of days bleeding gums in past 12 months	MMSE (3 assessments over 5 years) Dementia= If MMSE score <24 or doctor- or nurse-suspected dementia, referred to specialist for dementia evaluation, DSM-IV criteria Cognitive decline = drop ≥ 3 MMSE points by 3rd assessment	Age, sex, EQ-5D, socioeconomic, CVD risk factors: -behavioural -physiological -psychological	Hazard ratios	Fully adjusted Incident dementia (N = 109) Number of teeth (reference ≥22 teeth) 0 teeth (HR = 1.48, 95% CI = 1.24–1.78) 1–21 teeth (HR = 1.24, 95% CI = 1.05–1.46) Bleeding gums ≥12 days (HR = 1.19, 95% CI = 0.51–2.75) <12 days (HR = 0.42, 95% CI = 0.10–1.71) Cognitive decline (N = 1,806) Number of teeth 0 teeth (HR = 1.39, 95% CI = 1.21 –1.59) 1–21 teeth (HR = 1.23, 95% CI = 1.10–1.38) Bleeding gums ≥12 days (HR = 0.94, 95% CI = 0.77–1.15) <12 days (HR = 0.92, 95% CI = 0.75–1.13)
Tsakos et al., 2013 U.K.	Baseline: 1999&2001 for dental measures and 2002-03 for memory n = 3,166 M = 1,466; F = 1,700 Aged 60+ Follow-up: 10 years English Longitudinal Study of Ageing (ELSA), a national prospective cohort study	Longitudinal study	Self-reported (1999&2001): Those with some natural teeth (dentate) Vs. no natural teeth (edentulous)	Word recall test Immediate and delayed (range 0–20) Categorized according to memory performance: 1) poor memory category that included all those in the lowest quartile (≤6 words) 2) Other category includes all who recalled ≥ 7 words	Time, demographic characteristics, socioeconomic status, comorbidities, health behaviours, depressive symptoms, and anthropometric measurements	Generalized Estimating Equations (GEE)	For poor memory: the full model OR (95% CI) = 1.10 (0.87–1.39). Memory change: For continuous memory, the unadjusted model coefficient estimate (95% CI)= -0.46 (-0.70 to -0.22). The association was not significant after adjusting for socioeconomic status.

(Appendix B) Study reference	Population and sample	Study design	Oral health measures	Cognitive measures	Covariates	Statistical method	Main findings
Naorungroj et al., 2015 U.S.	n =911- Those who participated in the dental study at Visit 4 (1996-1998) and completed two cognitive assessments separated by 8 years (between 1996–1998 and 2004–2006) Average age: 64.7 at baseline Follow-up: 8 years The ARIC study	Longitudinal study	Oral examination (1996-1998): (1) number of teeth (2) Periodontal probing depth (3) Bleeding on probing biofilm–gingival interface (BGI) index used to classify periodontal disease	In 1996-98 and then 2004-06: (1) delayed word recall (DWR) (2) digit symbol substitution (DSS) (3) word fluency (WF)	Age, race, sex, educational level, income, study sites, cardiovascular risk factors, apolipoprotein E (APOE) genotype, stroke, and coronary heart disease (CHD)	Generalized Estimating Equations (GEE)	Complete tooth loss, not periodontal disease and number of teeth, was associated with low performance on two cognitive tests (DWR and WF) at baseline. Although all three cognitive scores declined over time, complete tooth loss, periodontal disease, and few teeth at baseline did not predict greater cognitive decline by any of cognitive measures.
Iwasaki et al., 2016 Japan	85 community-dwelling individuals Average age 79.3 years	Longitudinal study	Oral examination: severe periodontitis was defined as ≥ 2 interproximal sites with clinical attachment loss of ≥ 6 mm (not on the same tooth) and ≥ 1 interproximal sites with probing depth ≥ 5 mm	MMSE Either as binary variable (the drop of 3 or more scores) or as a continuous variable	Age, gender, education, depression, BMI, smoking status, alcohol use, exercise, hypertension, diabetes, and history of CVD and stroke	Poisson regression linear regression	the adjusted RR of incidence of a decrease of ≥ 3 points in MMSE score for participants with severe periodontitis was 2.2 (95% CI: 1.1–4.5) Participants with severe periodontitis had a 1.8-point greater decrease in MMSE score than did those without severe periodontitis (coefficient =-1.8; 95%CI:-3.3 to-0.2)
Li et al., 2017 China	8,153 participants Age 60+ interviewed in up to six waves.	Longitudinal study	Self-reported: Number of teeth.	MMSE	demographic characteristics, adult socioeconomic status characteristics, childhood socioeconomic status, health conditions, and health behaviours	Linear mixed models	More teeth were associated with better cognitive function (β = 0.01, P< .001). The interaction of teeth number and time was significant (β = 0.01, P< .001), suggesting that the participants who had more teeth showed a slower pace of cognitive decline over time than those with fewer teeth after controlling for other covariates.

(Appendix B) Study reference	Population and sample	Study design	Oral health measures	Cognitive measures	Covariates	Statistical method	Main findings
Petrovsky et al, 2019 US	2713 US Chinese older adults Age = 72.6 years on average Baseline: 2011-2013 Follow-up: 2015 The mean time was 1.92 years (SD = 0.30) (range = 1.75-3.72 y).	Longitudinal study	self-reported: Tooth and gum symptoms	Episodic memory ((Immediate and Delayed Recall of brief stories); executive function (Symbol Digit Modalities Test); working memory (Digit Span Backwards). Global cognitive function by constructing a composite measure	Sociodemographic and health-related factors measured at baseline.	Mixed-effect regression models	Having teeth symptoms at baseline experienced a faster rate of decline in global cognition for every additional year (estimate = 0.02; p = .047). This effect disappeared once adjusted for all covariates (estimate = 0.02; p = .069). No association found with gum symptoms.
Iwasaki et al., 2019 Japan	179 participants Age: 80.1 years on average Followed for 5 years 62 men and 117 women	Longitudinal study	Oral examination: Periodontal disease (severe vs. not severe) using two definitions.	MMSE	age, sex, smoking status, educational level, physical activity level, obesity, depression, and diabetes.	Multilevel linear mixed-effects mode	Participants with severe periodontal disease had faster cognitive decline in the fully adjusted model in both definitions.

Appendix C List of studies of the association between oral health and cognitive impairment

(Appendix C) Study reference	Population and sample	Study design and method	Oral Health Measures	Cognitive Measure	Covariates	Statistical method	Main findings
Shimazaki et al., 2001 Japan	1,929 residents of 29 institutions Average age 79.7 years	Longitudinal study (6 years follow up) Baseline on 1988-89 and follow-up at 1994-95	Oral examination: Two dentists recorded: number of teeth, and denture using. Dental status divided into 5 categories: ≥ 20 teeth, 1-19 teeth using dentures, 1-19 teeth not using dentures, edentulous using dentures, and edentulous not using dentures	From medical records: subjects who had no symptoms of dementia and cognitive disability at baseline, but had some symptoms of dementia or cognitive disability at follow-up, were defined as having deterioration in mental health	Age, physical health status, classification of institution, cerebrovascular disorder	Logistic regression analyses	The crude analysis showed significant high incidence of mental impairment among individuals with fewer teeth (1-19 teeth): The OR (95% CI) for those who use dentures 2.3 (1.0-5.1), and with no denture 4.4 (1.9-10.3) The crude analysis showed significant high incidence of mental impairment among edentulous individuals: The OR (95% CI) for those who use dentures 3.2 (1.5-6.8) and with no denture 5.2 (2.0-13.1) The associations were not significant in the multivariate analysis
Gil-Montoya et al., 2015 Spain	409 dentate, 180 cognitive impairment, and 229 no cognitive impairment Age 51-98 years	Case-control study 1) cases of firmed diagnosis of mild cognitive impairment or dementia of any type or severity (recruited from the Neurology department of 2 hospitals) 2) controls with no subjective memory loss complaints and a score >30 on the photo-test cognitive test (recruited from non-dental department in a primary care centre)	Oral examination: Four dentists recorded (1)tooth loss (as a proxy for periodontal disease) (2) plaque and bleeding indexes (3) probing depths (4)clinical attachment loss (AL) Both cases and controls were dentate	Assessed by a neurologist. For cases: (1) the DSM-IV for dementia, (2) the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for Alzheimer's Disease (3) the Spanish Society of Neurology Behavioural and Dementia Study Group for cognitive impairment For controls: Photo-test cognitive test	Age, sex ,education level, oral hygiene habits, hyperlipidemia	Logistic regression analyses	significant association was observed between AL and cognitive impairment after controlling for covariates The OR (95% CI) for moderate AL was 2.64 (1.18 to 5.92) and for severe AL 2.31 (1.15 to 4.66) No significant association was found between tooth loss and cognitive impairment

(Appendix C) Study reference	Population and sample	Study design and method	Oral Health Measures	Cognitive Measure	Covariates	Statistical method	Main findings
Stewart et al., 2013 U.S.	Baseline: 1997/1998 N = 947 Aged 70–79 M=~50%; F=~50% black 34%, white 66% Healthy Medicare community residents in local area, unimpaired basic ADL or mobility. Included all blacks, and random sample of whites Follow-up: Year 5	Longitudinal study (Looked at the association with cognitive impairment cross-sectionally and longitudinally and subsequent cognitive decline longitudinally)	Oral examination: (1) number of teeth (2) number of occluding pairs (3) mean probing depth (4) attachment loss (5) mean of gingival index (6) mean plaque score (7) number of bleeding sites on probing All measures categorized into quartiles for analysis	(1) Modified Mini-Mental State Examination (3MS) Y1, Y3, Y5): Cognitive impairment defined as core <80 of 3MS (bottom 10%, based on average at Y1&Y3) Cognitive decline defined as drop of ≥5 points of 3MS (most declining 20%) (2) DSST at Y1, Y5 (3) clock drawing at Y3 Cognitive impairment for both: bottom 10%	Age, sex, education, race, BMI, cardiovascular disease and risk, and depressive symptoms using CES-D score, CRP, Interlukin-6 at Y1, Weight loss at Y1 to Y3, Anticholinergic medications, APOEε4	Cognitive impairment and cognitive decline were modelled as binary dependent variables with quartiled oral health measures as primary independent variables, the latter entered into logistic regression models as ordinal variables	For the fully adjusted model, no significant association found between any dental measure and 3MS except for gingival inflammation (gingival index (GI) and plaque index (PI) scores) The OR (95% CI) for the mean GI at Y2 with cognitive impairment (from average 3MS from Y1&Y3) was 1.55 (1.17–2.06) and for the PI was 1.34 (1.05–1.72)
Okamoto et al., 2015 Japan	2,300 > 65 years cognitively intact and walk unassisted the Fujiwara-kyo study	Longitudinal study 5 years follow-up	Oral examination: Two dentists recorded: (1) number of teeth (healthy, carious, or treated) (2) Community Periodontal Index (CPI) code (3) the age at which edentulous individuals had lost all of their teeth	(1) MMSE (2) The Recall test (score range, 0-3)to assess recent memory Using these two measures and the Geriatric Depression Scale (GDS) to construct following groups: (1) “cognitively intact,” MMSE ≥ 24 plus a Recall score of 2 or 3; (2) “Mile Memory Impairment (MMI) status,” MMSE ≥ 24 plus a Recall score of 0 or 1, plus a GDS ≤ 5 (depression-free). (3) “suspected of pseudo-MMI induced by depression,” MMSE ≥24 plus a Recall score of 0 or 1 plus a GDS ≥ 6. (4) “cognitively impaired,” MMSE ≤ 23	Education level, drinking frequency, smoking habits, blood pressure, history of disease (cancer, myocardial infarction, cerebrovascular dis-ease, diabetes mellitus, hypertension, or dyslipidemia) and current medication	Multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were determined using logistic regression analyses (forced entry method)	After adjustment for the confounding factors, the OR of per 1 tooth loss at baseline was 1.02 (95% CI, 1.00–1.03). The ORs for the development of MMI in subjects with 17–24, 9–16, 1–8, and zero remaining teeth were 1.58 (95% CI, 1.12–2.25), 1.17 (0.73–1.88), 1.08 (0.64–1.80), and 2.39 (1.48–3.86),respectively, compared to sub-jects with 25–32 teeth (p for trend=0.020). Significant associations between having 17–24 teeth and MMI, and total tooth loss and MMI. A significant association was found between progressing to edentulism and the development of MMI.

(Appendix C) Study reference	Population and sample	Study design and method	Oral Health Measures	Cognitive Measure	Covariates	Statistical method	Main findings
Stewart and Hirani 2007 England	2463 in household (>65) and 1569 in care homes (>65) The Health Survey for England 2000	Cross-sectional study from secondary data	Self-reported: Either having some teeth or no teeth	Abbreviated mental test score composed of10 questions about orientation and memory: cognitive impairment defined if ≥ 3 incorrect response	Age, sex, and education, BMI, disability, and sampling area (community/care home)	Weighted logistic regression to assess the association Linear regression to assess the effect of dental status as mediator between cognitive impairment and BMI	Dental status and cognitive impairment highly associated. The OR (95% CI) of impaired cognition and edentulism was 2.80 (1.54–5.12). It was only significant in the community sample and almost null in the care home sample. Significant associations were found between cognitive impairment and lower BMI, for both samples, which does not suggest that measurement error in BMI was responsible for the lack of association with dental status (for the care home sample)
Okamoto et al., 2010 Japan	Control group (n = 3,696), Cognitively impaired (n = 214), Mild memory impairment group (n = 121) Age: > 65 years Used data from baseline examination in 2007-08 the Fujiwara-kyo study	Cross-sectional study	Oral examination: Two dentists recorded: (1) number of teeth (healthy, carious, or treated) (2) Community Periodontal Index (CPI) code (3) the age at which edentulous individuals had lost all of their teeth	(1) MMSE- used as a screening test for cognitive impairment. (2) The Recall test (score range, 0-3) used to evaluate the impairment of recent memory. Using these two measures and the Geriatric Depression Scale (GDS) to construct three groups: 1) Control group (n = 3,696) if MMSE>23 and scored 2-3 in Recall test 2) low MMSE if score of MMSE ≤23 (n = 214) 3) Mild Memory Impairment (MMI) if MMSE >23 and scored 0-1 in Recall test (n = 121)	Depressive symptoms, alcohol, smoking, walking time, visual and hearing impairment, ADL, CVD and chronic diseases, blood pressure, BMI, erological markers including serum albumin, haemoglobin A1c, cholesterol.	Logistic regression analysis (by the forced entry method) was carried out with MMI and a low MMSE score as dependent variables.	Significant relationships were found between number of teeth, the length of the edentulous period, and cognitive impairment. Significant relationships between number of teeth (per 1 decrease) and MMI, OR (95% CI)1.021 (1.001-1.041) and a low MMSE score, 1.039 (1.023-1.054) The OR (95% CI) for having 0-10 teeth compared to 22-32 teeth was for the MMI 1.679 (1.073-2.627) and for the low MMSE score 2.177 (1.510-3.140)

(Appendix C) Study reference	Population and sample	Study design and method	Oral Health Measures	Cognitive Measure	Covariates	Statistical method	Main findings
Saito et al., 2013 Japan	462 community-dwelling individuals. 163 males and 299 females, 60 years old or over The Iwaki Health Promotion Project	Cross-sectional study	Oral examination: Two dentists recorded: number of teeth and if teeth were healthy, carious, or treated.	MMSE: Poor cognition was defined as a score < 23	Age, gender, education level, smoking, drinking and medical history	Logistic regression analyses	After adjusting for confounding factors, 0–10 remaining teeth (OR = 20.21; 95%CI: 2.20 -185.47) was shown to be an independent risk factor for having poor cognitive level (≤23 MMSE)
Park et al., 2013 Korea	438 community-dwelling aged 50 years and older dementia and stroke free and apparently health	Cross-sectional study	Oral examination: Number of lost teeth: 0-5 and 6-10, >10 missing teeth	MMSE: cognitive impairment was defined as score <24	Age, gender, hypertension, diabetes, smoking and hyperlipidemia	Logistic regression analyses	Number of lost teeth was significantly related to cognitive impairment. The OR(95% CI) for those who lost 6 -10 teeth was 1.99 (1.08-3.69) and for those who lost more than 10 teeth was 2.26 (1.27- 4.02)
Nillson et al., 2014 Sweden The Swedish National Study on Aging and Care (SNAC)	1147 recruited from population-based multicentre cohort study (Age of selected sample 60-96 years)	Cross-sectional	Oral and radiographic examination: number of teeth: 0, 1-19, ≥20	(1) MMSE: cognitive impairment was defined as score <25. (2) Clock-test: individual asked to draw analogue clock and low cognitive function defined as score <8 out of 10	Age cohort, gender and level of education	Logistic regression analyses	Number of teeth significantly associated with cognitive impairment. The OR(95% CI) for those who were edentulous 3.2 (1.9-5.3), although not significant for having few teeth
Wang et al., 2014 Taiwan	2727 aged 65 years and older	Cross-sectional of secondary data	self-reported: (1) Number of lost teeth (2) dental prostheses (3) oral health status (4) self-limitation of food due to oral health status Number of teeth distributed to two groups either <20 teeth(n=1,053) or ≥20 teeth(n=1,233)	MMSE: Anyone scores >25 is normal and <10 is impaired and in middle is moderate dementia	Age, gender, BMI, education, marital status, family incomes, and lifestyle habits (smoking, consuming alcohol and the culture-oriented habit of chewing betel nuts)	Logistic regression analyses	The prevalence of low MMSE scores was significantly increased in association with decreases in the number of remaining teeth, suggesting that tooth loss may be associated with lower cognitive function The OR (95% CI) of having MMSE <25 was 1.54 (1.13, 3.9) for those who had <20 teeth (*p*=.006); however the association not significant after adjusting for covariates

(Appendix C) Study reference	Population and sample	Study design and method	Oral Health Measures	Cognitive Measure	Covariates	Statistical method	Main findings
Lexonboon et al., 2015 Sweden	557 aged >77 nationally representative of Swedish population	Cross-sectional study	Self-reported: Possible answers: "no teeth or only a few" "complete dentures or partial dentures," and "own teeth but in poor shape, i.e., many missing." Having natural teeth included "own teeth, many crowns, fillings, bridge," and "own teeth in good shape, few fillings". Multiple tooth loss was used as an independent variable instead of edentulousness. Chewing difficulty: "Can you chew hard food such as hard bread or apples?" The answer "Yes, without difficulty" was classified as not having chewing difficulty. The answers "Yes, but I must be careful" and "No, not at all" were classified as having chewing difficulty	A shortened version of MMSE: A score ≤ 12 out of a possible 18 corresponded to a score ≤ 23 on the complete MMSE and was used to identify persons with cognitive impairment	Age, gender, years of education and other illnesses such as depression, mental illness, and cerebral thrombosis.	Logistic regression analyses	Multiple tooth loss: The odds ratios (ORs) of cognitive impairment in persons with multiple tooth loss was 2.10 (P = .001) compared with persons with natural teeth, although the OR was not significant after adjusting for sex, age, and years of education Chewing difficulty: The simple logistic regression shows the OR of cognitive impairment in persons with chewing difficulty was 2.32 compared with persons without chewing difficulty (P < .001). The odds remained significantly higher when adjusted for sex, age, and education (OR = 1.82; P = .01) and when adjusted for history of depression and mental illness (OR = 1.72; P = .03)
Kim et al., 2017 Korea	295 elderly individuals aged >70 years	Cross-sectional study	chewing ability using gum that changed colour based on chewing performance	MMSE- Korean version.: normal or risk of impairment if score ≥21 and cognitively impaired if score ≤20	Age, sex, educational level, marital status. smoking , drinking, and treated disease. physical and instrumental activity of daily living (PADL and IADL) and Mini Nutritional Assessment (MNA)	Logistic regression analyses	Old participants with middle or low chewing ability had significantly higher risk of cognitive impairment. Association for low chewing only significant for unadjusted model OR (95% CI): 7.36 (2.91–18.60).

(Appendix C) Study reference	Population and sample	Study design and method	Oral Health Measures	Cognitive Measure	Covariates	Statistical method	Main findings
Iwasaki et al., 2015 Japan	291 Japanese (101 men and 190 women, average age: 80.9 years)	Cross-sectional study	Clinical examination: Attachment loss (AL) and the number of teeth. Three groups created: No periodontal disease (reference), periodontal disease, edentate.	MMSE. Cognitive impairment ≤ 23 and Hasegawa Dementia Scale-Revised (HDS-R) scores ≤ 20	Age, gender, years of education, body mass index, smoking status, drinking behaviour, and history of cardiovascular disease	Multivariable logistic regression	The multivariable adjusted odds ratios (ORs) (95% confidence intervals [CIs]) for low MMSE score associated with periodontal disease and were 2.21 (1.01–4.84) and with edentulous 2.28 (1.06–4.90 The multivariable adjusted ORs (95% CIs) for low HDS-R score associated with periodontal disease and edentulous were 4.85 (1.29–18.15) and with edentulous 3.86 (1.05–14.20)
Luo et al., 2015 China	3063 aged 60 or older in this community excluding those residing in a nursing home or other institution	Cross-sectional study	Self-reported: number of missing teeth confirmed by trained interviewer	Neurologist used several cognitive tests and applied the DSM-IV and Petersen criteria to create three groups: dementia, MCI or normal	Sex, age, education year, socioeconomic status, smoking, drinking and living status, BMI, anxiety, depression, heart disease, hypertension and diabetes and APOE	Logistic regression models	Losing > 16 teeth positively associated with dementia. The association of tooth loss and MCI was not significant after adjusting for confounders
Peres, 2015 Brazil	Participants (n= 1705) were 60 years of age and over, from a midsized Southern Brazilian city.	Cross-sectional study	Self-reported: 10 natural teeth, <10 natural teeth, no natural teeth (edentate)	Severe cognitive impairment was assessed with MMSE. ≤18 indicate severe cognitive impairment	Sex, age, educational attainment, equivalized monthly family income, self-reported colour/ race, smoking status, self-reported diabetes, cardiovascular disease, hypertension, and depression	multivariable logistic and partial ordinal logistic analyse	Edentate status was associated (OR 3.3; 95%CI 1.2, 9.3) with severe cognitive impairment in the fully adjusted model There was an interaction between number of teeth and age on severe cognitive impairment

(Appendix C) Study reference	Population and sample	Study design and method	Oral Health Measures	Cognitive Measure	Covariates	Statistical method	Main findings
Okamoto et al., 2017 Japan	537 Japanese subjects aged 65 years and over who were cognitively intact at baseline were analysed	Nested case-control study 2007 to 2012	Clinical examination: Number of teeth. 0–8, 9–16, 17–24, and 25–32 teeth Periodontal index	Mild memory impairment was defined by a clinical psychologists or a graduate student with a major in psychology as: (1) no impairment of the ADL; (2) normal general cognitive function, as determined using the MMSE, score ≥24; (3) presence of objective memory impairment, assessed by the Recall test, score ≤1; and (4) absence of depression	Age, sex, educational background, MMSE- total, Recall, Geriatric Depression Scale, smoking habit, history of cerebrovascular disease, myocardial infarction, hypertension, diabetes mellitus, hyperlipidemia and APOE	logistic regression	Having fewer teeth at baseline significantly was associated with higher odds of mild memory impairment
Iwasaki et al., 2019 Japan	79 community-dwelling dentate individuals (62 men and 117 women, average age: 80.1 years)	Longitudinal study	Oral examination: Periodontal disease (severe vs. not severe) using two definitions	MMSE After administering the MMSE, participants were examined by 3 neurologists. Participants were diagnosed with MCI if they fulfilled the following criteria:1 (a) subjective cognitive complaints; (b) memory problems that were abnormal for the participant's age noted during neuropsychological testing; (c) preserved functional ADL; and (d) failure to meet the DSM-IV criteria for dementia	Age, sex, smoking status, educational level, physical activity level, obesity, depression, and diabetes	Multilevel linear mixed- effects mode	Participants with severe periodontitis by either definition had significantly higher odds ratios (ORs) for MCI than those without
Sochocka et al., 2017	128 participants Age: 55 - 90 years	Cross-sectional	Clinical Examination: Bleeding on Probing for periodontal inflammation	MMSE	Age and sex	Correlations were assessed to assess the associations	Periodontal inflammation and cognitive impairment increase the level of systemic inflammation

Appendix D ELSA Cognitive Booklet: immediate and delayed word-list recall and animal naming

NatCen
Social Research that works for society

Head Office
35 Northampton Square
London EC1V 0AX
Charity no. 1091768

Operations Department
Kings House
101-135 Kings Road
Brentwood
Essex CM14 4LX
Telephone 01277 200 600
Fax 01277 214 117

Serial number | Ck | PerNo | First name:

Interviewer ID No. | Point No.

ELSA 50+ HEALTH & LIFE

COGNITIVE MODULE - INTERVIEWER RECORDING BOOKLET

Word List – First Recall

Please write down the words the respondent recalls in the space provided:

- Do NOT interrupt the respondent.
- If respondent is saying words more quickly than you can write them down in full, just write down the first letter of the word.
- Do NOT count any words the respondent says which are not on the list.

Word List A	Word List A - responses
Hotel	
River	
Tree	
Skin	
Gold	
Market	
Paper	
Child	
King	
Book	

Word List B	Word List B – responses
Sky	
Ocean	
Flag	
Dollar	
Wife	
Machine	
Home	
Earth	
College	
Butter	

Word List C	Word List C – responses
Woman	
Rock	
Blood	
Corner	
Shoes	
Letter	
Girl	
House	
Valley	
Engine	

Word List D	Word List D – responses
Water	
Church	
Doctor	
Palace	
Fire	
Garden	
Sea	
Village	
Baby	
Table	

18i_CogBooklet

(Continue Appendix D)

Animal Names

Please write down all the animal names given by the respondent in the space provided:

- Do NOT interrupt the respondent.
- If respondent is saying names more quickly than you can write them down in full, use abbreviations or a tally.
- ONLY if the respondent asks for clarification, explain that animals include birds, insects, fish etc.
- If the respondent gets stuck, say "Can you think of any more?"

Points to remember:

- Do NOT count repetitions
- Do NOT count redundancies (e.g. white cow, brown cow)
- Do NOT count named animals (e.g. Spot, Bambi)
- DO count different breeds (e.g. terrier, greyhound)
- DO count gender- or generation-specific names (e.g. bull, cow, heifer, calf)
- If the respondent names animals that are unfamiliar to you, give them the benefit of the doubt and **count them (e.g. Kudu)**

(Continue Appendix D)

Word List – Second Recall

Please write the words the respondent recalls in the space provided:

- Do NOT interrupt the respondent.
- If respondent is saying words more quickly than you can write them down in full, just write down the first letter of the word.
- Do NOT count any words the respondent says which are not on the list.

Word List A	Word List A - responses
Hotel	
River	
Tree	
Skin	
Gold	
Market	
Paper	
Child	
King	
Book	

Word List B	Word List B – responses
Sky	
Ocean	
Flag	
Dollar	
Wife	
Machine	
Home	
Earth	
College	
Butter	

Word List C	Word List C – responses
Woman	
Rock	
Blood	
Corner	
Shoes	
Letter	
Girl	
House	
Valley	
Engine	

Word List D	Word List D – responses
Water	
Church	
Doctor	
Palace	
Fire	
Garden	
Sea	
Village	
Baby	
Table	