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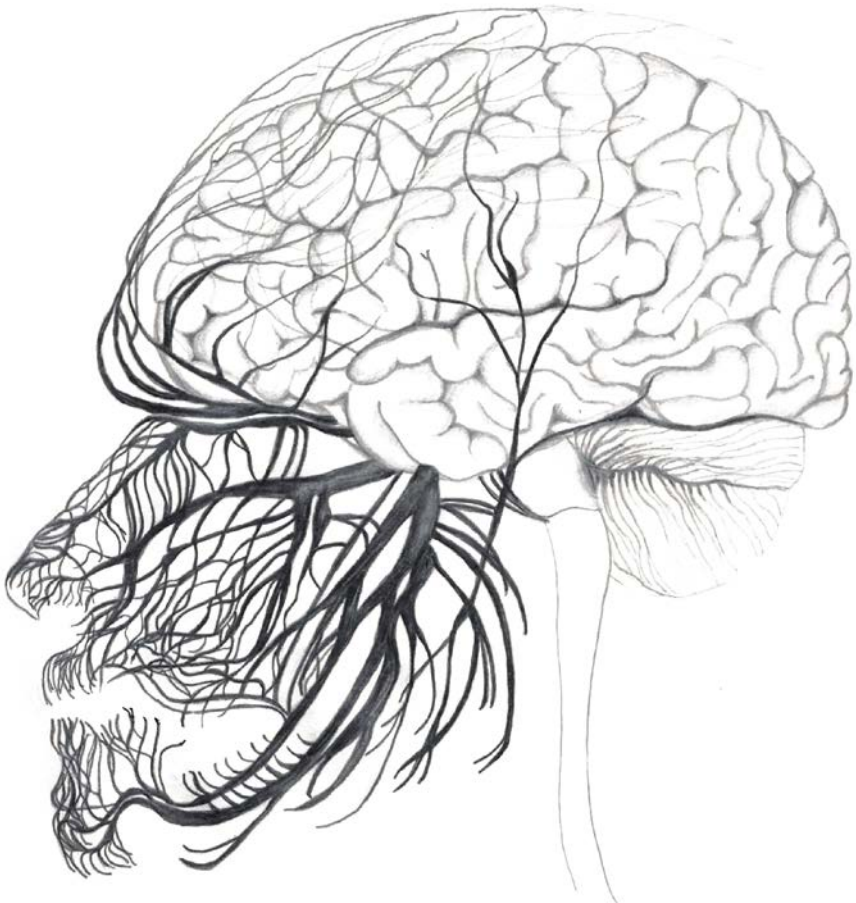
Oral Health & Olfactory Function: What can they tell us about Cognitive Ageing?



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ORAL HEALTH & OLFACTORY FUNCTION: WHAT CAN THEY TELL US ABOUT COGNITIVE AGEING?

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To my parents

"I don't believe in ageing. I believe in forever altering one's aspect to the sun."
Virginia Woolf

ABSTRACT

The objective of this thesis was to advance our understanding of whether oral health and olfactory function may predict accelerated cognitive ageing. Data from two Swedish study populations and one from the United States were applied to investigate the relationship of oral health and olfactory function with cognitive decline and brain ageing in late life.

Study I examined the association of self-reported tooth loss with cognitive decline, and brain volume differences in older adults (*n*= 2715) from the Swedish National study of Aging and Care-Kungsholmen (SNAC-K). A subsample (*n*= 394) underwent magnetic resonance imaging (MRI). Tooth loss was associated with a steeper global cognitive decline (β: -0.18, 95% confidence interval [CI]: -0.24 to -0.11). Participants with complete or partial tooth loss had significantly lower total brain volume (β: -28.89, 95% CI: -49.33 to -8.45) and grey matter volume (β: -22.60, 95% CI: -38.26 to -6.94). Thus, tooth loss may be a risk factor for accelerated cognitive ageing.

Study II Investigated the effect of poor masticatory ability on cognitive trajectories and dementia risk in 544 cognitively intact adults aged ≥50 from the Swedish Adoption/Twin Study of Aging (SATSA) with 22 years of follow-up. Masticatory ability was assessed using the Eichner Index and categorised according to the number of posterior occlusal zones: A (all four), B (3-1), and C (none). After the age of 65, participants in Eichner category B and C showed an accelerated decline in spatial/fluid abilities compared to those in category A (β: -0.16, 95% CI: -0.30 to -0.03 and β: -0.15, 95% CI: -0.28 to -0.02, respectively). Hence, poor masticatory ability is associated with an accelerated cognitive decline in fluid/spatial abilities.

Study III examined whether impaired olfaction is associated with cognitive decline and indicators of neurodegeneration in 380 participants (mean age = 78 years) from the Memory and Aging Project (MAP). Participants with hyposmia (β = −0.03, 95% CI: −0.05 to −0.02) or anosmia (β = −0.13, 95% CI −0.16 to −0.09) had a faster global cognitive decline than those with normal olfaction. Impaired olfaction was related to smaller volumes of primarily the medial temporal cortex (β = −0.38, 95% CI −0.72 to −0.01). Olfactory deficits predict faster cognitive decline and indicate neurodegeneration in older adults.

Study IV identified age-related trajectories in episodic memory and odour identification, as well as determinants of the trajectories. 1023 MAP participants were followed for up to 8 years with annual assessments. Three joint trajectories were identified; Class 1- stable performance in both functions; Class 2- stable episodic memory and declining odour identification; and Class 3- decline in both functions. Predictors of class membership were age, sex, *APOE* ε4 carrier status,

cognitive activity, and BMI. Episodic memory and olfactory function often show similar trajectories in ageing, reflecting their shared vulnerability to changes in the medial-temporal lobes.

Conclusions: Both poor oral health and olfactory deficits may predict cognitive decline and indicate neurodegeneration in the brain. Poor oral health is associated with accelerated cognitive decline and brain ageing, whereas, olfactory deficits may reflect loss of brain integrity in old age.

SAMMANFATTNING

Syftet med denna avhandling var att öka förståelsen för hur munhälsa och luktfunktion kan förutsäga accelererat kognitivt åldrande. Data från två svenska studiepopulationer och en från USA applicerades för att undersöka sambandet mellan munhälsa, luktfunktion och kognitivt åldrande.

Studie I undersökte sambandet mellan självrapporterad tandförlust och kognitiv nedgång, samt skillnader i hjärnvolym hos äldre vuxna (*n* = 2715) från Swedish National study of Aging and Care-Kungsholmen (SNAC-K). Ett undersampel (*n* = 394) genomgick magnetisk resonansavbildning (MRI). Tandförlust associerades med snabbare kognitiv nedgång (β: -0.18, 95% konfidensintervall [CI]: -0,24 till -0,11). Deltagare med fullständig eller partiell tandförlust hade lägre total hjärnvolym (β: -28.89, 95% CI: -49.33 till -8.45) och gråmaterialvolym (β: -22.60, 95% CI: -38.26 till -6.94). Således kan tandförlust vara en riskfaktor för snabbare kognitivt åldrande.

Studie II granskade effekten av tuggningsförmåga på kognition och demensrisk hos 544 kognitivt intakta vuxna i åldern ≥50 från Swedish Adoption / Twin Study of Aging (SATSA), uppföljda upp till 22 år. Tuggningsförmåga utvärderades med Eichner Index och kategoriserades enligt antalet ocklusala zoner: A (alla 4), B (3-1) och C (0). Efter 65 års ålder visade deltagare i Eichner kategori B och C en accelererad nedgång i frontala kogntiva förmågor (β: -0.16, 95% Cl: -0.30 till -0.03, respektive β: -0.15, 95% Cl: -0.28 till -0.02). Följdaktingen är sämre tuggningsförmåga associerat med en snabbare kognitiv nedgång av frontala förmågor.

Studie III undersökte om nedsatt luktförmåga är förknippad med kognitiv nedgång och hjärnatrofi hos 380 deltagare (medelålder = 78 år) från Memory and Aging Project (MAP). Hyposmi (β = −0.03, 95% CI: −0.05 till −0.02) (β = −0.03, 95% CI: −0.05 till −0.02) eller anosmi (β = −0.13, 95% CI −0.16 till −0.09) var associerade med snabbare kognitiv nedgång. Nedsatt luktförmåga var relaterad till mindre volymer av främst i mesio-temporalloberna (β = −0.38, 95% CI −0.72 till −0.01). Nedsatt luktförmåga förutsäger snabbare kognitiv nedgång och indikerar neurodegeneration hos äldre vuxna.

Studie IV identifierade åldersrelaterade banor i episodiskt minne och luktidentifiering, samt determinanter för olika banor. 1023 MAP-deltagare följdes i upp till 8 år med årliga utvärderingar. Tre banor identifierades; Klass 1- stabil prestation i båda funktioner; Klass 2-stabilt episodiskt minne och minskande luktidentifiering; och klass 3- nedgång i båda funktioner. Förutsägare för klassmedlemskap var ålder, kön, *APOE* ε4 status, kognitiv aktivitet och BMI. Episodiskt minne och luktfunktion visar ofta liknande banor i åldrande, vilket återspeglar deras delade sårbarhet för förändringar i medio-temporala lober.

Slutsatser: Både dålig munhälsa och nedsatt luktförmåga kan förutsäga kognitiv nedgång och indikera neurodegeneration i hjärnan. Dålig munhälsa är förknippad med snabbare kognitiv nedgång och åldrande av hjärnan, medan nedsatt luktförmåga kan återspegla förlust av hjärnintegritet hos äldre vuxna.

REZUMAT

Obiectivul acestei teze a fost de a sporii înțelegerea modului în care sănătatea cavității bucale și funcția olfactivă pot influența îmbătrânirea cognitivă. Populații de studiu suedeze și din Statele Unite au fost examinate pentru a reliefa relația dintre sănătatea cavității bucale, funcția olfactivă și declinul cognitiv.

Studiul I, a examinat asocierea dintre pierderea dinților și declinul cognitiv, precum și diferențele de volum ale creierului la adulții în vârstă (n = 2715) din studiul Swedish National study of Aging and Care-Kungsholmen (SNAC-K). Un subsexemplu (n = 394) a fost supus imagisticii prin rezonanță magnetică (RMN). Pierderea dinților a fost asociată cu un declin cognitiv global mai accentuat (β: -0.18, 95% interval de încredere [CI]: -0.24 până la -0.11). Participanții cu pierdere completă sau parțială a dinților au avut un volum total mai scăzut al creierului (β: -28.89, CI 95%: -49.33 până la -8.45) și volumul materiei cenușii (β: -22.60, CI 95%: -38.26 până la -6.94). Astfel, pierderea dinților poate fi un factor de risc pentru îmbătrânirea cognitivă accelerată.

Studiul II, a examinat efectul capacității de masticație asupra declinul cognitiv și a riscului de demență la 544 de adulți cu vârsta ≥50, din studiul Swedish Adoption / Twin Study of Aging (SATSA), monitorizați maximum 22 de ani. Capacitatea de masticație a fost evaluată folosind indicele Eichner și clasificată în funcție de numărul de zone ocluzale: A (toate cele 4), B (3-1) și C (0). După vârsta de 65 de ani, participanții la categoriile Eichner B și C au arătat o scădere accelerată a abilităților cognitive frontale (β: -0.16, CI 95%: -0.30 până la -0,03) și (β: -0.15, CI 95%: -0.28 până la -0.02). Capacitate de masticație mai slabă este asociată cu o scădere cognitivă mai rapidă a abilităților frontale.

Studiul III, a investigat dacă scăderea capacității olfactive este asociată cu declinul cognitiv și atrofiera creierului, la 380 de participanți (vârsta medie = 78 ani) din proiectul Memory and Aging (MAP). Hiposmia (β = −0.03, 95% CI: −0.05 până la −0,02) sau anosmia (β = −0.13, CI 95% −0.16 până la −0.09) a fost asociată cu declinul cognitiv mai rapid. Olfacția afectată a fost asociată cu volume mai mici, în principal în lobii mezio-temporari (β = −0,38, CI 95% -0,72 până la -0,01). Mirosul deteriorat reflectă un declin cognitiv mai rapid și indică neurodegenerarea la adulții în vârstă.

Studiul IV, a identificat traiectoriile memoriei episodice și identificării de mirosuri, precum și factorii determinanți ai acestei traiectorii. 1023 de participanți de la MAP au fost urmăriți până la 8 ani cu evaluări anuale. Trei traiectorii comune au fost identificate: Clasa 1- performanță stabilă în ambele funcții; Clasa 2- memorie episodică stabilă și identificarea de funcții olfactive în scădere și Clasa 3- declin la ambele funcții. Indicii de clasă au fost vârsta, sexul, *APOE* ε4 status, activitatea

cognitivă și BMI. Memoria episodică și funcția olfactivă prezintă adesea traiectorii similare în îmbătrânire, ambele reflectând vulnerabilitatea la schimbările lobilor medio-temporari.

Concluzii: Deficitul de sănătate cavității bucale, și deficitul olfactiv, pot indica declinul cognitiv și de asemenea neurodegenerarea creierului. Deficitele de sănătate ale cavității bucale, pot fi un factor de risc pentru deficiența cognitivă prin impactul negativ asupra creierului, în timp ce deficiențele olfactive pot reflecta pierderi ale integrității creierului.

LIST OF SCIENTIFIC PAPERS

I. **Dintica CS**, Rizzuto D, Marseglia A, Kalpouzos G, Welmer A-K, Wårdh I, Bäckman L, Xu W. Tooth loss is associated with accelerated cognitive decline and volumetric brain differences: a population-based study. *Neurobiology of Aging*. 2018; 67: 23–30.

II. **Dintica CS,** Marseglia A, Wårdh I, Rizzuto D, Shang Y, Xu W, Pedersen NL. The relation of poor mastication with cognitive trajectories: a population-based longitudinal study, (*Under review*).

III. **Dintica CS**, Marseglia A, Rizzuto D, Wang R, Seubert J, Arfanakis K, Bennett DA, Xu W. Impaired olfaction is associated with cognitive decline and neurodegeneration in the brain. *Neurology*. 2019; 92: e700–9.

IV. **Dintica CS**, Haaksma ML, Olofsson JK, Bennett DA, Xu W. Joint trajectories of episodic memory and odor identification in older adults: patterns and determinants, (*Submitted*).

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
APOE ε4	Apolipoprotein E gene-ε4 allele
BMI	Body mass index
CI	Confidence intervals
CIND	Cognitive impairment-no dementia
CNS	Central nervous systen
CVDs	Cardiovascular disorders
DSM	Diagnostic and Statistical Manual of Mental Disorders
ERC	Entorhinal cortex
GMV	Grey matter volume
HR	Hazard ratios
HV	Hippocampal volume
ICV	Intracranial volume
IPT	In-person testing
IR	Incidence rates
MAP	Memory and Aging Project
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
SATSA	Swedish Adoption/Twin Study of Aging
SD	Standard deviation
SES	Socioeconomic status
SNAC-K	Swedish National Study on Aging and Care-Kungsholmen
TBV	Total brain tissue volume
TIV	Total intracranial volume
VaD	Vascular dementia
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organization
WMHV	White matter hyperintensity volume
WMV	White matter volume

1 INTRODUCTION

Ageing is an experience that we as humans ubiquitously share, and with the developments in health care, we can expect to live longer than ever before. Nevertheless, each person follows their own individual trajectory, which may differ greatly from person to person. With advancing age, the human brain undergoes substantial structural changes [1]. Such brain changes may be accompanied by declines in cognitive performance that can be delayed by several decades [2–4]. Moreover, old age is characterised not only by an overall decline, but perhaps even more so by increasing variability in cognitive performance. An illustration of this can be seen in **Figure 1**, portraying the mean and individual cognitive trajectories from the Memory and Aging longitudinal project (MAP). The determinants of these individual differences may be conditions that are related to, but not necessarily consequences of old age. Classical views in cognitive science have considered cognition in abstraction from sensory processing and motor control. Nowadays, more emphasis is being put on how the world is experienced through mutual interactions between the physiology of the organism, its sensorimotor circuit and the environment [5].

Sensory impairments such as olfactory deficits, have been proposed as early signs of age-related changes in neurological functioning, neuropathology, or neurodegeneration, prior to decline in cognitive function [6–8]. Oral health is comparatively new to the stage of potential predictors for accelerated cognitive ageing; however, its potential as a modifiable risk factor is an exciting prospect, in particular from a public health perspective.

With the rise in people affected by dementia, and the numerous unsuccessful pharmaceutical trials, early screening and interventions for cognitive impairment remain our best alternatives. In this thesis, the relation of oral health and olfactory function with cognitive function, respectively, will be investigated.

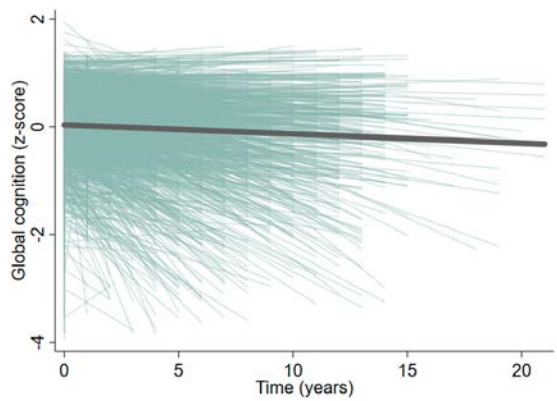

Figure 1. Trajectory of global cognition in adults with mean age 80 over 20 years. Data from the RUSH Memory and Aging project.

1.1 Cognitive ageing

We are now living longer than at any other time in history, as a result of the great advancements in our health care and living standards. It is therefore more important than ever to fully understand what distinguishes healthy cognitive ageing from pathological processes associated with ageing. In normal ageing, it is common to experience decline in so called fluid cognitive abilities like processing speed [9], executive function [10–12], and episodic memory [13–15]. On the other hand, so –called crystallised skills such as verbal ability and world knowledge, can be maintained well into advanced age [16]. In general, two overall trends are observed; an increase in acquired knowledge and skills until around age 60 followed by decline, and a nearly linear decrease from early adulthood for measures reflecting processing speed and efficiency [17–19]. In the Swedish Adoption/Twin Study of Aging (SATSA), it was observed that decline in perceptual speed, memory, and spatial fluid abilities started declining at 65, while verbal ability remained relatively intact until the age of 70 [27].

Findings from the Religious Order Study, show decline across all domains measured (memory, verbal ability, and visuospatial ability), accelerating with age [20]. Across all ages, however, wide individual differences were observed. Interestingly, the baseline function in each domain was not strongly associated with the rate of change in the respective domain, but there was a moderate association between the rates of change among the cognitive domains [20]. Wide individual variation in cognitive trajectories has frequently been reported [21–24]. These findings point to that cognitive change in older adults may reflect person-specific factors rather than being inherent to the ageing process. Such person-specific factors include accumulation of neurological and vascular insults affecting multiple cognitive systems, for instance, Alzheimer's disease (AD) pathology and cerebrovascular disease, but also the way an individual's system responds to such insults [25,26].

Brain morphology, just like cognition, has been associated with age-related change. In normal ageing, loss of volume is most evident in the frontal and parietal lobes and least in the occipital lobe [28–30], and may be limited in the medial temporal region including the hippocampus until middle or late adulthood [29,31,32]. In regards to white matter, there may be little volume change until the 40s or 50s, or possibly even an increase in volume with regional variation [33–36].

A multitude of studies have found relations between regional volume measures (adjusted for total intracranial volume) and global cognition or specific cognitive domains [37–43]. There are several reports associating frontal lobe volume of either grey or white matter with measures of fluid intelligence or executive functioning [44–50]. Volume-cognition relationships have also been observed between memory and medial temporal lobe volume, world knowledge with frontal and temporal volume [51], vocabulary knowledge with temporal lobe volume and inferior parietal volume [52,53], and digit symbol speed with parietal volume [51].

Based on the assumption that cognition is related to some extent with brain morphology, it would be reasonable to assume that any risk factor which negatively impacts cognition, should have a negative effect on brain structures related to the cognitive domain in question. Given that change in cognitive function in old age primarily seems to reflect person-specific factors, rather than an inevitable developmental process, it should follow that certain factors may affect the cognitive trajectory in ageing in either positive or detrimental ways.

1.2 Cognitive impairment and dementia

Dementia is one of the most devastating disorders, with huge impact on the individual and their families, as well as posing a great societal cost. It has been estimated that around 47 million people were living with dementia in 2015, and this number is expected to triple by 2050 [54]. According to criteria dating from 1994, a diagnosis of dementia requires an individual to have impairments in cognition, involving memory and at least one other cognitive domain, enough to interfere with daily activities. This definition is recommended by the American Academy of Neurology Guidelines [55].

Two common pathways underlying dementia disorders are vascular and neurodegenerative pathologies, corresponding broadly to vascular dementia (VaD) and AD dementia. AD is the most common neurodegenerative disorder, characterised by two main features: deposition of the amyloid-beta peptide (Aβ) in the brain and the formation of neurofibrillary tangles, composed of abnormally hyperphosphorelated tau [56]. AD is the most common cause of dementia syndrome (the behaviour/clinical manifestation consisting of cognitive symptoms and functional impairment), which includes AD dementia [56]. Based on large cohorts of cases confirmed post-mortem, a common characteristic of AD is substantial loss of brain volume, in particular in the medial-temporal lobe including the hippocampus. Brain atrophy is also prominent in inferior temporal and superior frontal gyri, while inferior frontal and orbitofrontal gyri, and occipital lobe are generally preserved. Data from in vivo studies using MRI have provided insights into the course of brain atrophy in AD [56].

For a patient to meet the criteria for VaD, cognitive dysfunction must be present, which may not include episodic memory. Most often the impairment includes slower information processing and executive dysfunction. Secondly, the patient should demonstrate cerebrovascular disease causally liked to the cognitive impairment, based on clinical stroke or vascular lesions on brain imaging, as cerebral small vessel disease (e.g. white matter hyperintensities) or large infarcts and haemorrhages [56].

Other definitions exist that apply to individuals with specific or milder forms of cognitive impairment, the most commonly used is mild cognitive impairment (MCI) [57]. The current diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) include two new syndromes; major neurocognitive disorder, including what is referred to as dementia, and minor cognitive disorder, describing individuals with mild cognitive deficits in one or more domain but who do not have major challenges to daily living [56].

1.3 Risk factors & predictors for cognitive decline & dementia

Considering the lack of effective treatment for dementia, let alone a cure, it is imperative for health care systems, as well as individuals themselves, to be aware of factors that may increase the risk. In recent years, many pharmacological trials targeting dementia have failed, therefore focus has shifted to life-style preventative strategies, based on empirical findings from epidemiological studies. In a recent review from Livingston et al. [54], the importance of prevention by targeting potentially modifiable factors was highlighted. At conception/early life, the apolipoprotein (*APOE*) ε4 allele and low education have been considered as risk factors; at midlife hypertension, obesity, and hearing loss are considered to increase risk; and at late life, social isolation, smoking, depression, physical inactivity, and diabetes are considered risk factors [54]. The *APOE* ε4 allele is a non-modifiable risk factor which increases the deposition of amyloid deposition in the brain and hinders its clearance, thereby contributing to neurodegeneration [58]. The other factors are potential targets for prevention and intervention as they are modifiable. However, in certain cases such as depression and hearing loss, it is unclear if these may be early markers of ongoing disease process, or risk factors, or both. Nevertheless, WHO had recently added hearing loss to the list of modifiable risk factors for dementia [59].

It is also important to consider that certain factors may have influence on the level, but not on the rate of change in cognitive function, and vice versa. An example is socioeconomic status (SES), whereby a lower SES has been associated with lower levels of cognition, but with no apparent contribution to the speed of cognitive decline [60] However, this may be subject to the timing of assessment, as a risk factor may act on cognition in early, mid, or late life. As will be discussed in the next sections, oral health and olfactory function have recently gained attention as predictive factors in cognitive decline. The distinction between a risk factor and a predictor of disease may be important depending on the context. In terms of prediction, the distinction may not be of large importance. Identification of predictors of the clinical transition to a diagnosis of dementia is important in order to estimate prognosis, which can be helpful for patients and family members.

However, if the aim is to develop preventative strategies and targets for interventions, it warrants a great deal of careful consideration, which will be addressed further in the discussion.

1.4 Definition of oral health & effects of ageing

WHO has defined health as "a state of complete physical, mental and social well-being and not just the absence of illness" [61]. This means that health is regarded as one multidimensional concept. This view of health includes both symptoms and physical functional ability, and emotional and social well-being [62]. The term also includes dental health as an important component of an individual's general health [63]. With this as a starting point, WHO has introduced the so-called Global Oral Health Program with the aim of integrating dental health in the prevention of chronic diseases and the promotion of public health [64].

There is no accepted definition of the concept of dental health, however, WHO defines oral health as below: "A condition free from chronic mouth and facial pain, oral and throat cancer, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders limiting the individual's bite, chewing, smile, and speech ability, as well as psychosocial well-being" [64]. The Swedish Dental Care Act (1985: 125) states that the goal of dental care is to maintain good dental health and provide care on equal terms for the entire population [65]. The regional Public Dental Service (Folktandvården) organisations are responsible for providing preventative dental care for children and young adults until age 23 [66]. The general dental support consists of a high-cost protection. The law of dental support for special groups (2008: 145) states that dental support must be provided for preventive dental care and for dental care that contributes to; cure pain or illness, the ability to eat, chew or talk without major obstacles and having an acceptable appearance [65].

Statistics from 2017 in Sweden showed that the number of remaining teeth among people aged 60-90 has increased by an average of 1.5 teeth. In the age group 60-74 years, the increasing number of teeth is made up of intact teeth, while in the age group 75-90 years, the increase in remaining teeth often applies to non-intact. With the number of non-intact teeth increasing, so does the need for preventive and restorative dental care [65].

Until recent times, most of the population could expect to become edentulous (lose all teeth) when entering the later part of life. Today, people are retaining teeth for longer and the proportion of the population with natural teeth has increased with each age cohort. Decay, periodontal disease, tooth loss, and masticatory problems, are however, still common in old age [67]. In the longitudinal population-based

Octogenarian Twin study, tooth loss in early life was related to lower social class, while in in middle age it was related to lower education, and in old age, to poor lifestyle factors and low social class [68]. Preservation of functional dentition into old age was attributed to non-smoking, higher education, being married and having good periodontal health [68]. Other contributing factors not mentioned in the above study include history of access to dentistry, knowledge of dental care, genetic predispositions, functional variations, or cognitive decline. In addition, medical use, in particular polypharmacy, can cause dry mouth (xerostomia), making the oral cavity more vulnerable to infection. The prevalence of edentulism (complete tooth loss) varies a lot across the world, however in Western Europe, it is overall 2% and peaks at around 15-23% in adults 65 to 85 years old [69].

1.5 Assessments of oral health

There are several measures of oral health including tooth loss, number of occlusal contacts, bite force, mixing ability, and the use of prostheses [70]. Tooth loss can be assessed simply by the count of remaining teeth, which may be intact or non-intact depending on the definition and may or may not include implants, however it does not include removable dentures. Masticatory function can be assessed in several ways; the comminution method involves test food being disintegrated into smaller pieces, with smaller particle sizes/volumes indicating better masticatory performance. The Eichner index, measures the number of posterior occlusal contacts in relation to masticatory ability. An individual is categorised according to the number of posterior occlusal (opposite teeth pair) contacts, which support the chewing process. Finally, the two-colour chewing gum method has been frequently used in studies, whereby the participant is given two chewing gums in different colours and these are qualitatively assessed according to how well the colours have blended during the chewing process [70].

Apart from assessing oral health functionally, it can be evaluated based on the presence of oral diseases or conditions such as gingivitis, caries, periodontal disease, or in rarer cases, oral cancer [71]. Such assessments must be made clinically by a dentist, however, in population-based studies, self-report of such conditions is common. Self-reported data can provide moderately valid estimates reflecting numbers of remaining teeth, dental treatments such as fillings, root canal therapy, and fixed and removable prostheses. However, they are deemed less reliable for the assessment of dental caries and periodontal disease [72]. Self-report of masticatory function has also been used in some studies, however, this has shown to have a weak correlation with objective masticatory performance [70].

1.6 Oral health & cognition

Several studies have shown that poor oral health is associated with steeper global cognitive decline [73,74], and an increased risk for cognitive impairment [75–78] and dementia [79,80]. One cross-sectional study found that jaw mobility, bite strength and complaints about masticatory function were associated with variation in episodic memory and executive function [81]. Other studies have reported negative findings regarding the relationship between cognition/dementia and dental status [82–87]. Methodological limitations may explain the inconsistent findings, such as small sample sizes, cross-sectional designs, short follow-ups (in particular for dementia as outcome), selected populations, and key confounders not taken into account. Therefore, it is not clear if the relationship between poor oral health and cognitive function could be independent of other related factors such as overall poor health status.

Tooth loss is often an indication of ongoing or past oral inflammation, which has been proposed as a trigger of systemic inflammation and atherosclerotic conditions, such as cardiovascular diseases (CVDs) and cerebrovascular disease [88–91]. Nevertheless, the role of systemic inflammation and vascular disease burden in the relationship between tooth loss and cognitive decline remains unclear. Moreover, volumetric brain changes after tooth loss have been observed in mice [92], indicating a possible direct effect of tooth loss on the brain. However, studies on the relation between tooth loss and brain ageing in humans are lacking.

Studies in mice have shown that masticatory dysfunction, due to soft diets or tooth loss, induced spatial memory, and learning deficits [93–96]. Moreover, neurogenesis in the hippocampus is suppressed in mice with tooth loss [97–99]. In humans, a cross-sectional study showed that poorer mastication is related to worse executive functioning, as well as reduced cerebral blood flow to the prefrontal cortex, responsible for higher order cognitive processes [100]. Only two studies examined the relationship between mastication and cognitive function or dementia longitudinally [101,102]. One study reported a steeper decline in those with fewer posterior occlusal pairs over 3 years in 80 year-olds [101]. However, cognitive function was measured using the Japanese version of the Montreal Cognitive Assessment, and therefore there was no indication of the longitudinal effects of mastication on specific cognitive domains, which could elucidate potential mechanisms involved. Yamamoto et al., reported no increased risk of dementia over 4 years in participants with poorer self-reported mastication [101].

1.7 Overview of the olfactory system & effects of ageing

Olfactory impairments are frequently observed in older populations, with a prevalence of 13.9% in individuals >65 years old, to over 50% in individuals between 65 and 80 years old, and up to 80% in those >80 years of age [103,104]. Indeed, one of the most robust findings in normal older adults is impaired odour identification [105]. There are several age-related changes which can impair olfactory function. These include nasal diseases, loss of odourant-selective receptor cells, reduction in mucosal metabolising enzymes, and neurochemical changes in the brain [106]. Furthermore, age related changes in nasal air flow patterns, mucous composition, increased prevalence of chronic rhinosinustis, nasal polyposis, and lessened mucocilliary can limit the access to olfactory receptors [104]. Moreover, atrophy and pathology in the central olfactory processing areas have been implicated in reduced olfactory function before death in neuropathological studies, and in-vivo neuroimaging findings [107,108]. Several functional MRI studies have also found reduced activation in odour processing areas in older participants [109–113].

Olfactory dysfunction may be present early in neurodegenerative diseases such as AD, and may therefore act as an important early clinical symptom of neurodegeneration [103]. However, it may not be a specific to AD, as olfaction has seen to be impaired in a variety of other neurological diseases including Parkinson's disease (PD), schizophrenia, multiple sclerosis, and epilepsy [104,114]. As such, olfactory functioning has been proposed as an indicator of the integrity of the ageing brain [103].

1.8 Assessments of olfactory function

Olfactory function can be evaluated through different types of assessments, such as psychophysical tests, e.g. odour detection, identification, discrimination, as well as electrophysiological and functional brain activations in response to odorants [104]. Olfactory impairment in older populations have been most commonly identified using psychophysical tests, which require a conscious response on the part of the participant. Odour identification tests are the most commonly used psychophysical tests. Different versions of the identification test exist, such as the 40-item University of Pennsylvania Smell Identification Test (UPSIT) and its briefer 12-item version (the Brief Smell Identification Test or B-SIT). In these tests, the participant is presented with familiar odours, and should then identify the name of the odour from several alternatives in a forced choice manner. The odours should be familiar, therefore, identification tests are often modified to include odourants and choice alternatives familiar to populations in a given culture [115]. Odour threshold tests can be considered equivalent to pure-tone hearing threshold tests, where the stimuli consist of a range of concentrations of an odorant, rather than a range of tones. In these tests, the participant is asked to differentiate sets of odours or odour mixtures by detecting the "odd" stimulus [104].

A meta-analysis concerning the different olfactory assessments in AD dementia and PD showed that PD patients have more deficits on lower-level perceptual tasks, while AD dementia patients perform poorer in higher-order olfactory tasks requiring the recruitment of specific cognitive processes, such as odour identification [116]. Considering the above findings and previous studies showing the strong practical implications of odour identification on daily life in older adults, as well as its association with episodic memory [117], it is likely the most relevant olfactory measure to detect subclinical cases in AD dementia.

1.9 Olfactory function & cognition

In recent years, several studies have shown an association of impaired olfactory function with cognitive impairment [117–124] and dementia [119,125–128]. One of the earliest symptoms of AD dementia is dysfunction in olfactory discrimination and odour recognition memory [129,130]. Brain structures implicated in AD pathology, involving the olfactory system such as the entorhinal cortex (ERC) and hippocampus, exhibit significant pathology and atrophy [107,108, 131-135]. This is further reflected in the correlation between odour identification and volumetric loss of the hippocampus [136]. Limited research has been conducted on the association between olfaction and cognition in a general population of older adults, not at high risk for dementia. A few longitudinal population-based studies have found that poorer olfactory performance is associated with cognitive decline [120,122,128,137,138], however there is need for studies with longer follow-up time. Moreover, with the exception of two studies [120, 139], most studies have not addressed the possibility of underlying dementia pathology driving the associations between olfactory impairment and cognitive decline. Therefore, the cognitive trajectory in dementia-free older adults with olfactory impairment remains uncertain.

Not much is currently known about the neurobiological mechanisms that underlie the relationship between olfactory and cognitive performance in cognitively normal older adults. Odour discrimination and identification involves the hippocampus, pointing to its intimate relationship with memory [140]. Therefore, recent focus has been put on finding neurological substrates of olfactory impairment in older adults. The central olfactory system projects to several regions in the medial temporal lobe, such as the hippocampus and ERC, involved in episodic memory function [103]. Studies have shown that worse olfactory function is associated with smaller hippocampal volume in mild cognitive impairment and AD dementia patients [136,141,142]. Moreover, previous work with cognitively normal participants, reported abnormal AD signature cortical thickness and lower volumes in the hippocampus, ERC and amygdala and markers of neurodegeneration such as elevated cortical amyloid, and CSF markers of neuronal injury in participants with olfactory impairment [108,143,144]. However, previous studies on structural brain

differences in relation to olfactory impairment in older adults are few and have focused on specific AD markers, such as the hippocampus and ERC.

Moreover, the APOE ε4 allele has been associated with olfactory impairment [145], and accelerated cognitive decline [146], as well as conveying a higher risk of AD dementia [58]. It has therefore been implicated in the relationship between olfactory impairment and cognitive decline, with one study finding an accelerated cognitive decline only in *APOE* ε4 carriers [146], whereas another suggests that *APOE* ε4 and olfactory impairment exert independent effects on cognitive trajectories [147]. Older adults with at least one *APOE* ε4-allele, demonstrate greater decline in odour identification than non-carriers [148]. This was observed even after controlling for verbal ability and general cognitive status, indicating that the influences of ε4 allele on odour identification are independent of clinically established dementia [148].

Only a few studies thus far have examined the longitudinal relationship between olfaction and episodic memory [139, 149–150]. One study reported that fluctuations in episodic memory corresponded to fluctuations in odour identification over time, particularly for individuals with AD pathology [149]. In a study investigating "change-change" correlation in episodic memory and odour identification, the correlation was only seen in *APOE* ε4 carries, specifically ε4 homozygotes [150]. This is consistent with the notion that ε4-carriers with AD dementia, compared to non-carriers, display a cortical atrophy pattern that is more focused on medial temporal cortical regions, supporting olfactory and episodic memory functions [151].

1.10 Theoretical considerations

There are several theoretical frameworks and perspectives from which this thesis could be discussed. For both oral health and olfactory function in relation to cognition, three main themes are evident; the inflammation hypothesis, the sensory deprivation hypothesis and the common cause hypothesis. The inflammation premise or "inflamm-aging" theory as it has also been referred to, states that pathogens either endogenous to the body or from the periphery, enter the body from in this case, the nasal or oral cavities, which then trigger an immune-response and upregulated inflammatory processes in the peripheral nervous system as well as in the central nervous system (CNS) [152,153]. This is a normal and healthy response, however, if the source of inflammation is for example a chronic state of infection, it may either itself negatively impact the CNS through neurotoxic processes and neuronal death, or through exasperating already present pathological processes such as AD pathology.

The sensory deprivation theory in the context of ageing, states that bodily functions including sensory and cognitive functions [6,7], are vulnerable to the principle of

"use it or lose it": i.e. if a function deteriorates from either its peripheral or central constituents, the associated nerves and brain areas will atrophy with time. In regards to oral health, this could apply to trigeminal nerve deafferention, a term referring to the loss of enervation from the nerve terminals after events such as tooth loss or severe damage [154,155]. In the case of olfaction, the chemosensory changes in the nasal cavity, olfactory bulb and its higher projections could also lead to under activation of higher order olfactory processing areas. Moreover, neuroplastic changes caused by altered perceptual and sensorial feedback may result in chronic reallocation of cognitive resources, which in turn could affect cognitive performance over time.

Lastly, the premise of the "common cause" hypothesis is that in late life, a common, biologically based factor is able to account for much of the age-related variance in sensory, sensorimotor, and intellectual functioning [156]. This could include AD pathology, age-related atrophy or a specific disease. In this thesis, the common cause paradigm could be applied to explain the association between oral or olfactory performance to that of cognitive outcomes.

Importantly, these theories are not mutually exclusive and certain aspects may be more relevant to specific parts of this thesis, which will be addressed in the discussion.

1.11 Knowledge gaps

For oral health and olfactory function to be considered as predictors or risk factors of accelerated cognitive decline, certain questions need to be addressed. In the case of oral health, there is a need for further longitudinal studies regarding the association between different types of oral health measures and cognitive decline. In addition, more consideration for possible factors involved in this relationship, such as vascular disease, inflammation, SES, overall health status, and functional ability, is necessary to elucidate potential mechanisms.

Regarding olfactory function, further evidence is warranted concerning whether olfactory impairment is associated with cognitive phenotypes and brain atrophy patterns specific to AD dementia. Moreover, examining whether episodic memory and odour identification have joint vs distinctive age-related trajectories, and which factors determine these patterns, could shed light on the nature of the close relationship between these functions. Such classification would contribute to a better understanding of the factors related to cognitive decline and dementia.

2 AIMS

2.1 General aims

1. Investigate if different oral health measures are associated with accelerated decline in general cognition and specific domains in a dementia-free sample.
2. Explore if poor dental health is associated with lower brain volumes.
3. Confirm which cognitive domains are most associated with olfactory impairment and how this is reflected in levels of brain atrophy in dementia-free older adults.
4. Examine the trajectories of episodic memory and olfactory function over time and which factors could influence stability or decline in these functions.

2.2 Study specific aims

Study I

1. Investigate the longitudinal association between tooth loss and cognitive decline, using 9-year follow-up data from a population-based cohort study, and examine the role of inflammation and vascular diseases, in this association.
2. Explore the cross-sectional relationship between tooth loss and structural brain differences, using MRI.

Study II

1. Assess the relationship between poor masticatory function (reduced posterior occlusal support) and cognitive trajectories in different domains.
2. Examine the risk of dementia associated with masticatory function using longitudinal data from a population–based study with up to 22 years of follow-up.

Study III

1. Confirm the association between olfactory impairment and cognitive decline in different domains using 15-year follow-up data.
2. Investigate the association between olfactory impairment and neurodegenerative markers assessed with structural MRI.

Study IV

1. Characterise trajectories of episodic memory and odour identification over 8 years in older adults.
2. Identify the determinants of trajectories in episodic memory and odour identification.

3 METHODOLOGY

3.1 Study populations

3.1.1 Swedish National study on Aging and Care-Kungsholmen (SNAC-K)

The Swedish National study on Aging and Care-Kungsholmen (SNAC-K) is part of a larger, national, longitudinal, multi-purpose study in Sweden – the Swedish National study on Aging and Care (SNAC) that started in 2001 [157]. The study involves four research centers collecting data in four different areas of Sweden. SNAC-K participants consist of a random sample of individuals aged 60 years and older living at home or in institutions in the Kungsholmen district, a central area in Stockholm, Sweden. The participants were taken from 10 different age cohorts beginning at the age of 60 up to the age of 96 years. Assessments took place at 6-year intervals for younger cohorts (60, 66, and 72 years), and at 3-year intervals for older cohorts (78+ years). SNAC-K has been linked with the national hospital registers and the death register.

SNAC-K population for Study I

Of the 5111 persons initially invited to participate in SNAC-K, 4590 were alive and eligible, and 3363 (73.3%) agreed to take part in the baseline survey (March 2001 through June 2004). Of the 3363 baseline participants, we excluded 310 participants with prevalent dementia/questionable dementia, 41 with neurological/developmental disorders, 282 with missing data on dental status, and 15 with missing MMSE score, leaving 2715 participants for the analytical sample (**Figure 2**).

3.1.2 The Swedish Adoption/Twin Study of Aging (SATSA)

The Swedish Adoption/Twin Study of Aging (SATSA) [158] originates from the population-based Swedish Twin Registry (STR) [159], which was initiated after the discovery that a number of twins had not been reared together. This was further investigated, and a first questionnaire (Q1) was subsequently sent out in 1984 to both the reared apart twins and a sample of twins reared together, matched on birth year, birth county and sex. Out of the 2 845 who received Q1, 71% responded (n=2 018). Participants in SATSA are part of both the old cohort (born 1886–1925) and middle cohort (born 1926–1958) in the STR. The data was obtained through mailed questionnaires and in-person testing (IPTs). A total of 9 questionnaires have been sent out between 1984 and 2014. The first IPT was carried out in 1986-1988 and those twin pairs who both had responded to Q1 and were 50 years or older were invited to participate in the study. The IPTs included extensive health assessments, including a cognitive battery, physical and functional health examinations. A total of 859 individuals have participated in at least one IPT and 76% have participated in three IPTs or more [158].

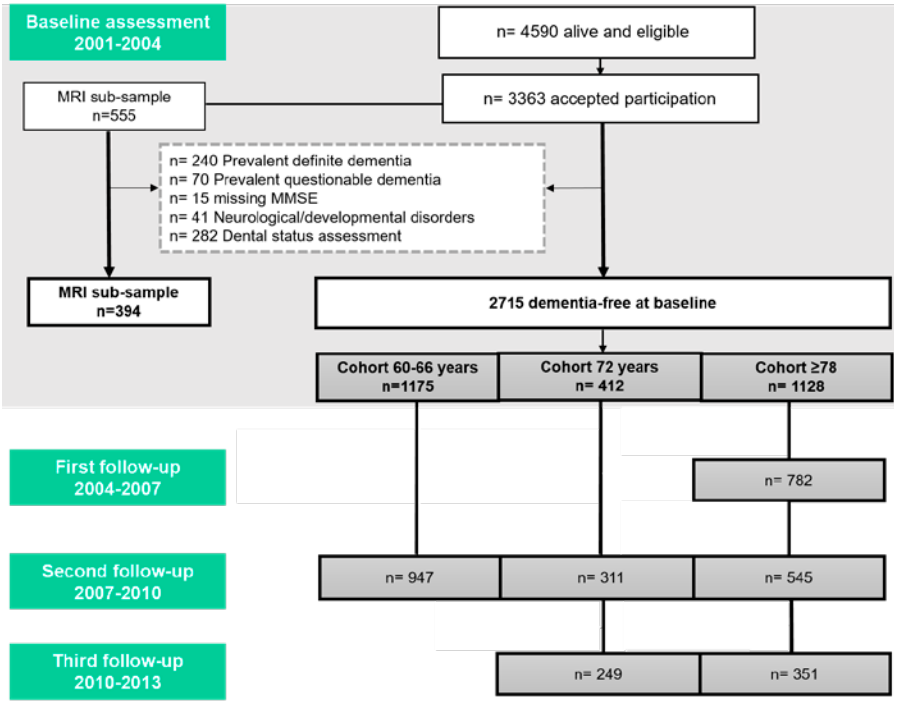

Figure 2. Flowchart of the study population in Study I.

SATSA study population in Study II

Information on dental status was collected during IPT2 (1989-1991), therefore, only the participants who were assessed at IPT2 were included in this study (*n*=595), henceforth referred to as the baseline. *Study II* was therefore based on data from IPT2 to IPT 9, spanning 22 years of follow-up. After excluding participants with missing information on dental status (*n* = 5), prevalent dementia (*n* = 8) or cognitive impairment no dementia (CIND) at baseline (*n*=38), 544 dementia-free participants remained for the analytical sample (**Figure 3**).

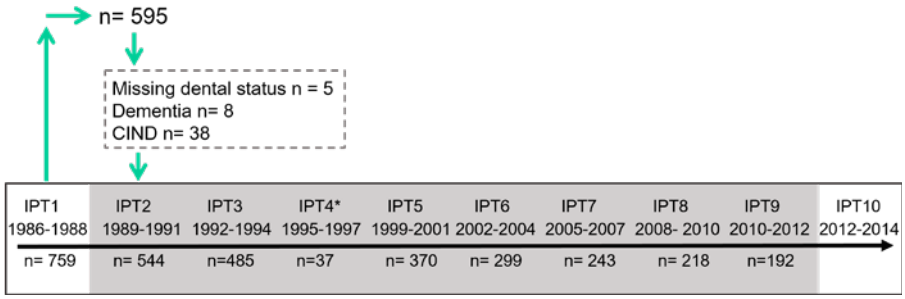

Figure 3. Flowchart of SATSA Study II sample. *Only a subset of the participants was assessed at IPT4.

3.1.3 The Memory and Aging Project (MAP)

The Rush Memory and Aging Project (MAP) started in 1997 and is an ongoing longitudinal clinical-pathologic study of risk factors for common chronic conditions of old age [160]. Eligibility requires agreement to annual clinical evaluations and to the donation of brain, spinal cord, and selected nerves and muscles to Rush investigators at death. In brief, participants from the greater Chicago area were recruited from retirement communities, senior citizen housing facilities, church groups, and senior centres. At the time of enrolment and thereafter, all participants underwent extensive clinical evaluation, including medical history, neurological examination, and detailed cognitive function testing [160].

MAP study population in Studies II and IV

From the total sample recruited up until 2012 (*n*=1919), we restricted the sample to participants who underwent an MRI examination (420) and further excluded those with prevalent dementia at baseline (*n*= 6), prevalent PD (*n*= 3) and with missing odour identification assessment at baseline (*n*= 31), leaving 380 participants for the analytical sample of *Study III*. The annual odour identification assessment began in 2011, therefore, this acted as analytical baseline for *Study IV*. From the total number recruited by 2018 (*n*= 2022), we restricted the sample to those who had at least two assessments starting 2011 (*n*= 1041) and further excluded participants who had prevalent dementia (*n*=18) (**Figure 4**).

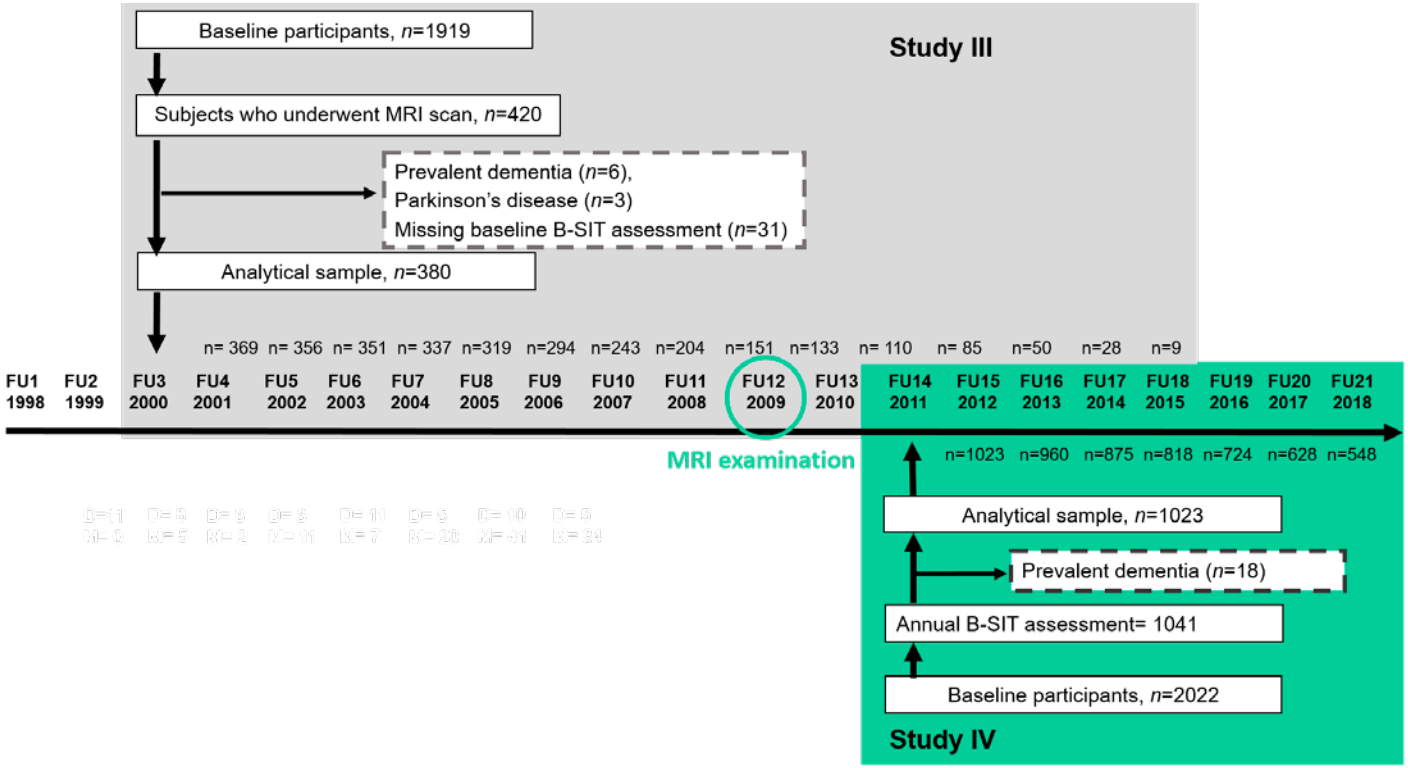

Figure 4. Flowchart of MAP Study III and IV samples. Abbreviations: FU= follow-up. B-SIT= Brief Smell Identification.

3.2 Data collection & definitions

3.2.1 Cognitive measures & dementia diagnosis

SNAC-K

Cognitive functioning was assessed at baseline and at each follow-up with the Mini-Mental State Examination (MMSE). This is the test used to measure global cognitive functioning [161], with a maximum of 30 points. A score less than 24 is generally considered to indicate cognitive impairment [161]. The test includes questions about different functions such as orientation to time and place, attention, calculation, memory, language, and visuospatial ability. Dementia diagnosis was carried out according to following the DSM-IV criteria at baseline and at follow-ups, using a validated 3-step procedure. Two physicians independently made a preliminary diagnosis and, in case of discordant diagnoses, a third opinion was sought from a senior physician [162]. According to the DSM-IV, participants who fulfilled all the criteria were classified as "definite" dementia and as "questionable" dementia when impairment in memory or other cognitive abilities was questionable.

SATSA

The cognitive battery included 12 tests assessing four cognitive domains: verbal abilities (information, synonyms, and analogies), spatial/fluid (Figure logic, Kohs Block Design, and Card rotations), memory (Digit span forwards and backward, Thurstone's pictures memory, Name and faces immediate and delayed recall), and perceptual speed (Symbol digit, and Figure identification) [163]. These domains were identified by principal–component analysis (PCA) [164]. Briefly, cognitive assessments at each wave were standardised using the means and variances observed at baseline. For each wave, a factor representing each cognitive domain was generated by combining the standardised cognitive scores using the factor weights derived from the PCA at baseline. A cognitive component was created based on the first principal component of the cognitive tests. All component scores were rescaled as t-scores by adding a constant of 50 and multiplying by 10 [165].

CIND was considered as the condition where the observed cognitive deficits were not severe enough to meet the criteria for dementia diagnosis. A person was categorised has having CIND if the person's MMSE at study entry was at least 1 SD or 2 SDs below the age- and education-specific mean MMSE in people aged 50-75 years or ≥75 years, respectively [166]. Dementia was diagnosed at follow–up examinations according to criteria from the DSM–III or DSM–IV [164,167]. Clinical diagnosis of dementia was determined during a consensus meeting, in which performance on cognitive tests, health, daily functioning, and medical records were reviewed [168].

MAP

From 2009, a sub-set of MAP participants underwent MRI scanning. Cognitive function was assessed at study entry and annual follow-up examinations, with a battery of 21 tests in an approximately 1-hour session [169]. Briefly, episodic memory was tested using the immediate and delayed recall of the East Boston Story, Story A from Logical Memory and Consortium to Establish a Registry for Alzheimer's Disease Word List Memory, Recall, and Recognition. Visuospatial ability was assessed with a 17-item version of Standard Progressive Matrices and a 15-item version of Judgment of Line Orientation. Perceptual speed was tested using Number Comparison, the Stroop Test, and the oral version of the Symbol Digit Modalities. Semantic memory was assessed by a 15-item version of Extended Range Vocabulary, a 20-item reading recognition test from the National Adult Reading Test, a 20-item version of the Boston Naming Test, and Verbal Fluency test. Working memory was tested using Digit Ordering, Digit Span Backward, and Digit Span Forward. The scores on each test were converted to z scores (based on all MAP participants at baseline) [169]. The z scores from component tests were averaged to yield a composite score for global cognition [169]. Dementia was diagnosed following the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [160].

A summary of all cognitive assessments and dementia diagnoses used in this thesis is available in **Appendix Table 1**.

3.2.2 Brain MRI measures

SNAC-K

MRI examination was available in a sub-sample of 555 participants (**Figure 2**). Participants were scanned with a 1.5T MRI scanner (Philips Intera, The Netherlands). The protocol included an axial 3D T1-weighted fast field echo (repetition time [TR] 15 ms, echo time [TE] 7 ms, flip angle [FA] 15°, field of view [FOV] 240, 128 slices with slice thickness 1.5 mm and in-plane resolution 0.94 × 0.94 mm, no gap, matrix 256 × 256), and an axial turbo fluid-attenuated inversion recovery sequence (FLAIR; TR 6000 ms, TE 100 ms, inversion time 1900 ms, FA 90°, echo train length 21, FOV 230, 22 slices with slice thickness 5 mm and in-plane resolution 0.90 × 0.90 mm, gap 1 mm, matrix 256 × 256).

The volumes of grey matter (GMV), white matter (WMV), and cerebrospinal fluid were derived after segmentation of the T1-weighted images in SPM12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, FIL, London, UK), implemented in Matlab 10 (The Mathworks Inc., MA, USA), using the improved unified segmentation algorithm that employs an extended set of tissue-probability maps [170]. The "light cleanup" option was used to further remove odd voxels from the images. Total brain volume (TBV) was obtained by summing GMV

and WMV. Hippocampal volume (HV) was computed with automated segmentation of the T1-weighted images performed with the Freesurfer 5.1 image-analysis suite (http://surfer.nmr.mgh.harvard.edu/) [171]. White matter hyperintensities volume (WMHV) was manually drawn on FLAIR images by a neuroimaging expert and further interpolated on the corresponding T1 images to compensate for the gap between slices in FLAIR (the intra-rater reliability was high [ICC >0.987]) [172]. Total intracranial volume (TIV) was calculated by adding the GMV, WMV, and cerebrospinal fluid volumes. All segmentations were inspected by the SNAC-K neuroimaging expert. All MRI volumetric measurements were normalized by TIV and age [1].

MAP

From 2009, a sub-set of MAP participants underwent MRI scanning. High-resolution T1-weighted anatomical data were obtained on a 1.5-tesla GE (General Electric, Waukesha, WI) MRI scanner, using a 3-dimensional inversion recovery prepared fast spoiled gradient recalled sequence with the following parameters: echo time = 2.8 milliseconds (ms), repetition time = 6.3 ms, preparation time = 1,000 ms, flip angle 8°, field of view 24 × 24 cm, 160 slices, 1-mm slice thickness, 224 × 192 image matrix reconstructed to 256 × 256, 2 repetitions [173]. FreeSurfer (v.5.0) was used to automatically segment the MRI data. When necessary, manual intervention was used to increase the accuracy of labelling. Whole-brain grey matter volume as well as the volumes of cortical and subcortical grey matter structures were obtained [174,175]. Total volumes (adding left and right sides) were calculated and converted from cubic millimeters to tenths of percentage of intracranial volume (using the estimate of intracranial volume from FreeSurfer v.5.0). There were 19 participants who were scanned at a different site; therefore, the site of scanning was included as a covariate in all analyses.

3.2.3 Oral health assessments

SNAC-K

Dental health was assessed during the nurse interview at baseline, with the following question: “Do you have your own natural teeth only or removable denture?”, with the possible answers: (1) own teeth only; (2) own teeth with removable denture; (3) own teeth with removable denture in one jaw and full denture in one jaw; (4) complete tooth loss; (5) complete tooth loss and full denture in one or both jaws; or (6) implants. Based on these alternatives, we categorised dental status as: a) no tooth loss (1), b) partial tooth loss (2; 3; 6), or c) complete tooth loss (4; 5), and these categories were used in the analyses [176]. Masticatory ability was assessed with the following question: “Can you chew hard food such as hard bread or apples?” The answer alternatives were (1) yes, without difficulty; (2) yes, but I must be careful; and (3) no, not at all. These answers were categorised as (1) no chewing difficulty; (2) having mild chewing difficulty; and (3) having severe chewing difficulty.

SATSA

During IPT2, trained nurses examined and recorded the presence/absence of each tooth and type of filling if present. The nurses also collected information using a questionnaire about whether the participants used prostheses, categorised as none, half-prosthesis or whole prosthesis. Additionally, the participants were asked if they have problems with gingivitis (bleeding gums; no/yes or sometimes) or periodontal disease (yes/no).

Each participant was categorised according to the Eichner Index [177]. In the Eichner classification, each posterior contact, including both the premolar and molar regions, are counted as one zone, yielding a total of four supporting zones [178]. The Eichner Index describes the existing posterior occlusal support zones by dividing the occlusal status into three main groups (A, B and C). Individuals classified in Group A have occlusal contacts in all four posterior support zones (indicating optimal masticatory ability), those in group B have 1-3 occlusal contacts (indicating moderate masticatory ability) and those in group C have no posterior occlusal contact at all (indicating poor masticatory ability). The categorisation was checked for errors independently by I.W. (DDS, specialist in Orofacial medicine) for a random 10% of the sample.

A summary of oral health measures and proportions in SNAC-K and SATSA is available in **Appendix Table 2**.

3.2.4 Olfactory function assessment

MAP

Odour identification was first assessed in MAP in 2000 and then annually after 2011. The Brief Smell Identification Test (B-SIT) (Sensonics. Inc., Haddon Heights, USA) was administered to test odour identification. The B-SIT is a standardised test with 12 items, each with 4 alternatives. The test consists of a booklet, where each page contains a scratchable patch of microencapsulated odourant. For each item, the examiner scratched the odour patch with a pencil which releases the odourant, placed it under the participant's nose, and asked which of four specific odours the sample most closely resembled. The participant must choose one odour. The scoring consists of the number of correctly identified odours, with possible scores ranging from 0-12. For each missing item response to a maximum of two, a score of 0.25 was assigned, corresponding to a chance level performance [169]. If responses to three or more items were missing, data on this test were considered as missing. The content of the B-SIT has been shown to be internally consistent, and scores correspond well to the 40-item UPSIT from which it was derived [169].

3.2.5 Covariates

SNAC-K

Data on demographic factors (age, sex, and education) and lifestyle factors (smoking and alcohol consumption), were collected through personal interviews by nurses following a structured protocol (http://www.snac-k.se/). Educational level was categorised into elementary school, high school, or university and above. Smoking status (non-smokers for those who had never smoked, former smokers, or current smokers) and alcohol consumption (low/never, moderate, or heavy) were trichotomised [170]. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. As a measure of functional ability, walking speed was tested by asking participants to walk 6 meters in their usual pace, or 2.4 meters if the participant reported walking quite slowly, and recorded in meters per second. In this test, a walking aid was allowed [179].

Chronic diseases, including diabetes and CVDs (including heart failure, arrhythmia, bradycardias and conduction diseases, cardiac valve disease, and ischemic heart disease), were ascertained from examinations by physicians, self-reported medical history, medication use, or linkage with the Swedish National Patient Register. The 10th revision of the International Classification of Disease was used in the registry. Multimorbidity was defined as the presence of 2+ chronic diseases [180]. Peripheral blood samples were taken from all participants. *APOE* allelic status was dichotomized into any epsilon 4 (ε4) carriers or ε4 non-carriers [181]. Haemoglobin (Hb) and albumin (Alb) were measured as markers of nutritional status. Hb was measured using the sodiumlauryl sulphate method (Sysmex XE-5000, Sysmex Corp, Kobe, Japan). World Health Organization criteria for the diagnosis of anaemia (Hb concentration <130 g/L in men and <120 g/L in women) was used to dichotomise serum Hb levels [182]- Alb was measured by bromocresol purple dye method (DXC800, Beckman Coulter, Brea, CA, USA) and hypoalbuminemia was defined as Alb concentrations <37 g/L [183]. C-reactive protein (CRP) was measured as a marker of inflammation at baseline and at follow-ups, using a turbidimetric method (DXC800, Beckman Coulter) and was dichotomized as normal (0-5 mg/L, lab reference value) or high (>5 mg/L).

SATSA

From the original questionnaire in 1984, information on demographics (i.e., education) was available and lifestyle factors (i.e., smoking, alcohol consumption, and physical exercise) were collected at each wave through IPT5. Nurses measured blood pressure, weight, and height at baseline and at each follow–up examination. Information on medical conditions (e.g. hypertension, heart diseases), and medication use was obtained through self–report at baseline and each follow-up

examination. Specifically, hypertension was defined as resting blood pressure ≥140/90 mmHg, and/or self-reported use of antihypertensive medication [184]. Heart disease was coded as the self-reported presence of any of the following: myocardial infarction, heart failure and angina pectoris. Blood samples were taken at study entry and *APOE* gene was genotyped utilising high-throughput sequencing and dichotomised as any ε4 carriers or ε4 non-carriers.

Educational level was dichotomised as low (elementary or vocational, ≤ 9 years) and high (high school or above, >9 years). BMI was calculated as weight in kilograms divided by squared height in meters (kg/m2) [185]. Smoking status was categorised as non–smoker (participants who had never smoked), past smoker and current smoker. Alcohol consumption was dichotomised as never-drinker (never drink alcohol) and drinker (former and current drinker). SES in childhood (rearing home) was measured from a scale including three components: material resources within the household, highest education of the parents, and highest occupational status of the parents. This scale was based on factor analyses. Variables were standardized to a mean of 0 and a standard deviation of 1 before summing. A higher score on the scale reflects higher SES level [60].

MAP

All participants underwent a uniform evaluation by trained staff through structured interviews, clinical and neurological examinations, and cognitive testing [160]. Data on socio-demographic characteristics (i.e., age, sex, and education), lifestyle factors (i.e., smoking), medical conditions, and cognitive function were collected at each wave following standardised procedures [160]. Education was recorded as maximum years of formal schooling. Smoking was categorised as "never smoked", "former smoker" and "current smoker". Information on medical conditions including heart disease, hypertension, diabetes was collected based on self-report during the interview at baseline. BMI was calculated as weight in kilograms divided by squared height in meters (kg/m2). Blood samples were taken at study entry and the *APOE* gene was genotyped utilising high-throughput sequencing and participants were stratified as ε4 carriers or ε4 non–carriers. Depression was determined according to the criteria of the DSM-III-R, implemented with a subset of questions from the Diagnostic Interview Schedule at baseline. All participants were asked "In the past month, has there been a period of 2 weeks or more during which you felt sad, blue, or depressed, or when you lost interest and pleasure in things you usually cared about?" A yes response elicited questions about the presence of 8 other symptoms of depression during this period (e.g., lack of appetite, lack of sleep, low energy, lack of concentration, guilt), and the presence of 4 or more of these additional depressive symptoms led to a diagnosis of major depression [186].

3.3 Statistical analysis

In this thesis, linear regression, multinomial logistic regression, linear mixed-effects model, growth mixture modelling, and Cox regression were used (**Table 1**). Point estimates are presented with 95% confidence intervals (CI) or standard error (SE), in order to provide information on the variability of the data and the precision of the estimate. The confidence intervals were calculated using the point estimate and the estimated standard error under the assumption of normality. The range of the CI depends on the sample size, the SE and the confidence level. A narrower confidence interval or lower SE indicates better precision, while a larger CI indicates more uncertainty. If the confidence interval includes zero, it is generally assumed that the point estimate is not statistically significant, i.e., not distinguishable from zero. In Cox regression, a hazard ratio above 1 indicates that the exposure is positively associated with the event probability, and thus negatively associated with the length of survival.

3.3.1 Linear regression

Linear regression is one of the simplest forms of regression analysis. In this thesis linear regression was used to test the cross-sectional relationship between tooth loss and MRI volumetric measures in *Study I* and the relationship between olfactory function and MRI volumetric measures in *Study III*.

3.3.2 Multinomial logistic regression

Multinomial logistic regression is an extension of linear regression analysis used when the dependent variable is categorical with more than two levels, and can be used for predictive analysis. This regression analysis was used in *Study IV*, where a set of predictor variables were used to predict class membership 1,2, or 3 of trajectories in episodic memory and odour identification.

3.3.3 Linear mixed-effects model

The linear mixed-effects model (LMM) is similar to linear regression, with the added benefit of being able to handle longitudinal and clustered or hierarchical data, i.e. when there is non-independence in the data. In this thesis, the LMM was used in *Study I* to test the effect of tooth loss on cognitive decline over 9 years, in *Study II* to test the effect of Eichner category on cognitive decline in different domains over 22 years, and in *Study III* to test the relationship between olfactory function and cognitive decline over 15 years.

3.3.4 Growth mixture model

The growth mixture model (GMM) is a longitudinal form of latent class analysis, in which mixed models are used. The GMMs therefore allow for grouping of subjects into so-called latent classes, on the basis of similarities in their progression patterns over time. The GMM was used in *Study IV* to model trajectories of episodic memory and odour identification score separately and jointly over time. Each participant is given a probability of class membership. These class memberships are informative in themselves as the allow for visualisation of trajectories in episodic memory and odour identification and estimate their correlation, as well as proportion of individuals who fall into different trajectory patterns. This can be taken a step further by predicting class membership on the basis of certain factors, e.g. sex, age etc.

3.3.5 Cox proportional hazards model

Cox regression is a method to estimate survival using time-to-event data. In *Study III*, Cox regression was used to estimate the association between Eichner categories and the risk of dementia diagnosis over 22 years. Cox regression estimates hazard ratios (HRs) across an underlying time scale, under the assumption that hazards are proportional for all levels of the predictor over time. This can be tested with Schoenfeld's residuals regressed against follow-up time. The HRs are ratios of event rates between different exposure groups.

Table 1. Analytical methodology used in the doctoral project by study.

	Study I	***Study II***	***Study III***	***Study IV***
Study population	SNAC-K	SATSA	MAP	MAP
Analysis **Method**	*Tooth loss-cognitive decline:* Mixed models	*Olfactory impairment-cognitive decline*: Mixed models	*Eichner categories-cognitive decline:* Mixed models	*Episodic memory-odour identification:* Growth mixture models
	Tooth loss-brain volumes: Linear regression	*Olfactory impairment -brain volumes:* Linear regression	*Eichner categories-dementia risk:* Cox proportional hazards model	*Predictors of trajectory classes:* multinomial logistic regression

3.4 Ethical considerations

SNAC-K and SATSA received ethical permissions (registration numbers are reported in from the Ethics Committee at Karolinska Institutet and the Regional Ethical Review Board in Stockholm. The MAP study was approved by the institutional

review board of Rush University Medical Center (**Table 2**). Participants also signed a repository consent that allowed their data to be shared. Informed consent (written or oral) were collected from all participants in SNAC-K, SATSA, and MAP prior to their inclusion in the study, in accordance with the ethical principles for medical research involving humans stated in the World Medical Association's Declaration of Helsinki.

In SNAC-K, participants were informed both by letter and in person. Two weeks before assessment, a letter was sent to explain the study's purpose and duration, interview process, and the importance of participation. Participants were informed that participation was voluntary and that they could withdraw at any time and without explanation. If a person had cognitive impairment, a proxy (i.e., close family member or guardian) was asked for consent. Afterward, nurses telephoned only those who agreed to participate and scheduled an appointment. The examination process took place in a friendly and comfortable environment. During the examination, if the participant expressed anxiousness or discomfort, the interview was terminated. As part of the informed consent process, participants were assured that their data would remain confidential and anonymous.

Similarly, in SATSA, all participants received a letter that described the purpose, content, and duration of the study and were assured confidentiality and anonymity as part of the informed consent process. Participants were informed that their involvement in the study was voluntary and that they were free to drop out at any point in time.

For data collected through the registry system, ethical requirements clearly state that the consent must be voluntary. This means that information on the health status of participants who dropped out was not available from registries, with the exception of data on vital status (if participants was alive or died), which is not covered by privacy law. Risks to privacy have been further minimised by assigning one administrator to access the registries and limiting the information accessible. In all datasets, researchers obtained anonymized data without any reference to a person's name or personal identification number; data were tagged with only a study-specific ID number.

In MAP, permission to access patients' full medical records including computerized medicare records was requested. Confidentiality of those records and all other information obtained in this study are maintained by labelling the information with a numeric code. A computer file and a paper document linking this code to the participants' identity will be located separately and will be accessible only to authorized study personnel. Participation in the study is voluntary and participants can withdraw at any time without affecting their care. Participants may withdraw from any individual component of the study (the clinical evaluation, the storage

bank, the blood draw, or removal of tissue after death). If they withdraw, participants also have the option of asking that data already collected be removed from the data files. Participants do not waive any legal rights by signing this consent document. Any and all personal and medical information provided by the participants will be confidential. However, a monitor or auditor for the Rush Institutional Review Board or other regulatory authorities will have access to these records for verification of research procedures, without violating confidentiality. The Institutional Review Board is a special committee that reviews human research to check that the rules and regulations are followed.

There is very little risk or discomfort associated with participation in any of the three studies. Participants might find the testing procedures stressful. The blood draw may cause mild discomfort and/or leave a bruise, or may cause fainting and the possibility of infection. There are no known significant risks with the MRI procedure because the radiowaves and magnetic fields used by the machine are thought to be harmless. The sole exception is if a cardiac pacemaker or a certain type of metallic clip (such as a brain aneurysm clip) is present. Therefore, to be eligible for MRI examination, the participants fill out a questionnaire including if such metal objects are present in the body. The MRI machine makes a loud, knocking noise. This may be mildly annoying, but poses no risk because the participants' ears are well-protected. Some participants can experience mild claustrophobia while in the scanner and they may discontinue the scan at any time.

Table 2. Ethical approvals for SNAC-K, SATSA and MAP.

Study	Registration/ORA numbers
SNAC-K *Study I*	01-114; 04-929/3; Ö 26-2007; 2010/447-31/2; 2009/595-32
SATSA *Study II*	84:61; 98-319 ; 2010/657-31/3
MAP *Study III*	L99032481-CR10
Study IV	L86121802-CR12

4 RESULTS

4.1 Oral health & cognitive decline/dementia

4.1.1 Tooth loss and MMSE decline

In *Study I*, 2715 dementia-free participants of age >60 years were followed for up to 9 years. The prevalence of any tooth loss was 22.5%, including 14.9% for partial loss and 7.6% for complete tooth loss. Compared with participants with no tooth loss, those with partial or complete tooth loss were more likely to be older and smokers, have more vascular diseases, hypoalbuminemia, anaemia, CRP level above 5 mg/L, multimorbidity, slower walking speed, and lower education and baseline MMSE score.

Over the 9-year follow-up, both partial (β: -0.13, 95% confidence interval [CI]: -0.20 to -0.05) and complete (β: -0.30, 95% CI: -0.42 to -0.18) tooth loss were significantly associated with steeper MMSE decline, compared with no tooth loss after multi-adjustment. In the multi-adjusted model, any tooth loss (partial or complete) was associated with an increased decline of 0.18 (95% CI: -0.24 to -0.11) MMSE score per year, compared with the no tooth loss (**Figure 5**).

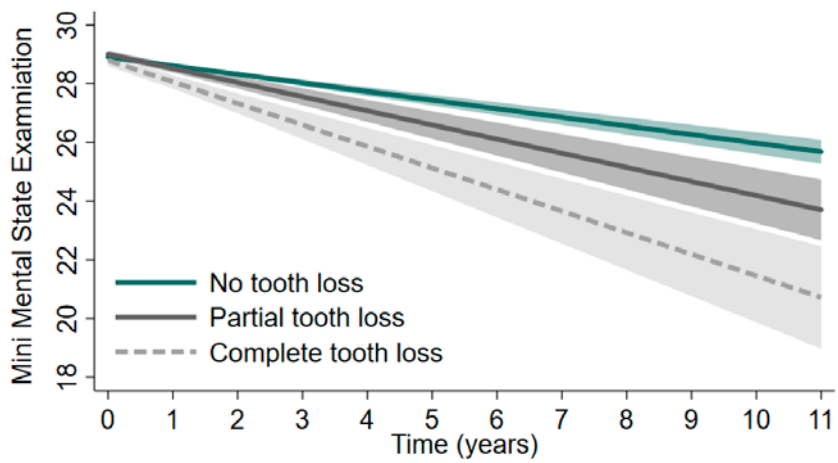

Figure 5. Estimated annual mean change in MMSE score by tooth loss over 9 years. Model adjusted for age, sex, and education, smoking, alcohol consumption, multimorbidity, walking speed, *APOE* ε4 allele status, anaemia, hypoalbuminemia, diabetes, time-varying C-reactive protein levels, CVDs, and cerebrovascular disease.

Furthermore, stratified analyses by CVDs, cerebrovascular disease, and CRP >5 mg/L were performed. The direction of the tooth loss cognitive decline association

was not affected by CVDs or CRP stratification, and the association became non-significant among people with cerebrovascular disease, likely due to lack of power.

Moreover, we adjusted and stratified by occupational status dichotomised as blue collar (*n*= 596) or white collar workers (*n*= 2116). Further adjustment of occupational status had no effect on the estimates. The association between tooth loss and cognitive decline in white collar workers was similar to that in the main sample (β= -0.21, 95% CI: -0.36 to -0.05 for partial tooth loss; β= -0.31, 95% CI: -0.53 to -0.10 for complete tooth loss), and while the association was in a similar direction, it was not significant in the blue collar workers (β= -0.16, 95% CI: -0.36 to 0.03 for partial tooth loss; β= -0.22, 95% CI: -0.47 to 0.04 for complete tooth loss) likely due to loss of power.

4.1.2 Masticatory function and trajectories in cognitive domains

In *Study II*, we categorised participants according to the Eichner Index in the SATSA study sample (*n*=544), according to number of posterior occlusal contacts. People in Eichner category A have all 4 occlusal contacts, B have 3 to 1 occlusal contacts, and C have none. The number of participants in Eichner category A was 147 (27.0%), 169 in category B (31.1%), and 228 (41.9%) in category C. The median follow-up time was 10 years, inter quartile range (IQR)= 16-3.

Participants in Eichner categories B and C, compared to those in those in Eichner A, were older and had lower educational level. Moreover, participants in Eichner category C specifically, consumed less alcohol, had lower education and childhood SES, and had higher proportions of belonging to the early birth cohort, having heart disease, hypertension, wearing prosthetics, and periodontal disease.

In the basic-adjusted model (sex, education, birth cohort, and practice effects), compared to participants in Eichner category A (optimal masticatory ability), those in category B had a lower performance in verbal ability at intercept (β: -0.18, CI: -0.26 to -0.11) (**Figure 6, panel C**). Moreover, participants in category B and C had steeper declines in spatial/fluid abilities after age 65 (β: -0.16, 95% CI: -0.30 to -0.03) and (β: -0.15, 95% CI: -0.28 to -0.02), respectively (**Figure 6, panel A**).

There was no significant difference between Eichner category A relative to B or C in the intercept or slopes for perceptual speed, memory, or the cognitive component score (**Figure 6, panels B, D, E**). After further adjustment for hypertension, heart disease, periodontal disease, prosthesis use, childhood SES, and alcohol consumption, the association between Eichner category B and verbal ability intercept remained significant, as did the association between Eichner category B and C with spatial/fluid abilities slope after age 65.

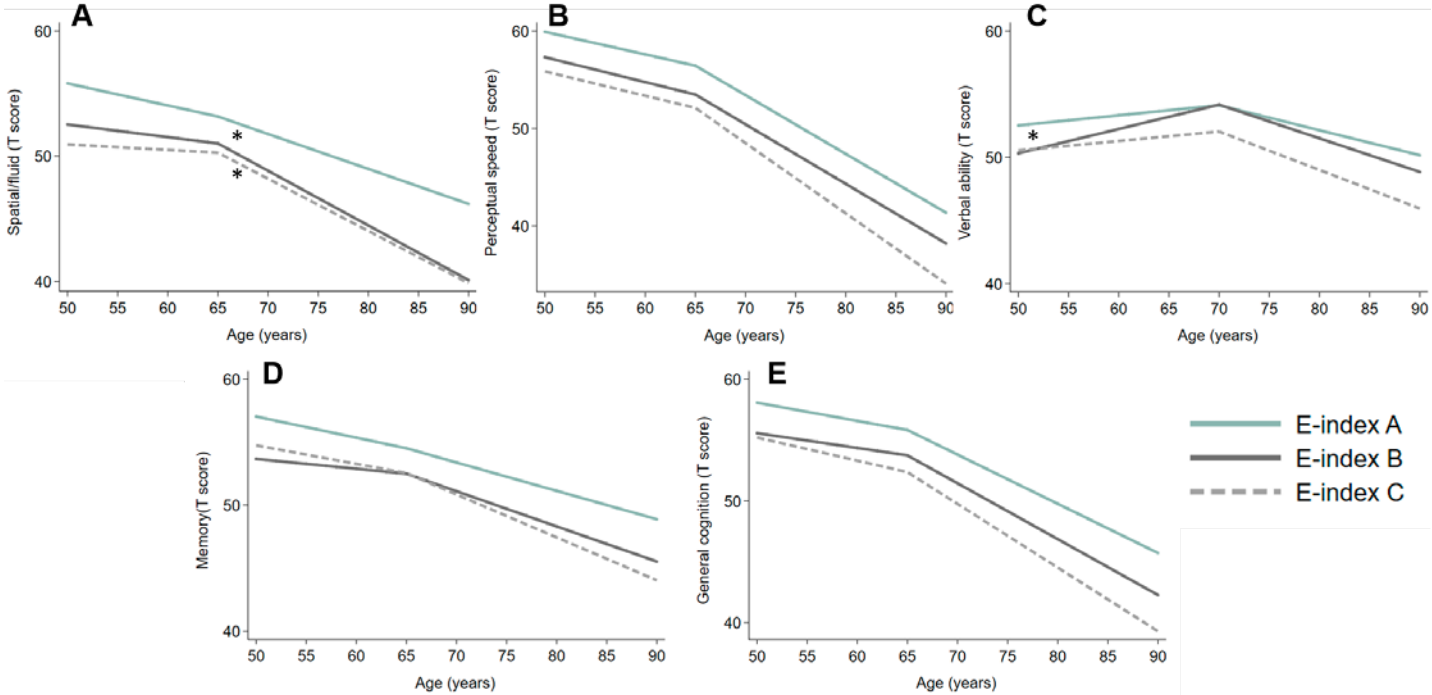

Figure 6. Cognitive trajectories in different domains by Eichner categories. Mixed models with age as timescale, adjusted for sex, education, birth cohort, and practice effects (n=544). Reference= Eichner A. A knot was placed at age 65 (spatial/fluid abilities, memory, and perceptual speed) or at age 70 (verbal ability). A) Spatial /fluid abilities; B) Perceptual speed; C) Verbal ability; D) Memory; E) General cognition.

We further wanted to explore if childhood SES had an impact on the relationship between Eichner category and decline in cognitive domains. An interaction term Eichner index*age*childhood SES was included in the main model; we did not find an interaction at intercept or for the slope of cognitive decline in any of the cognitive domains.

4.1.3 Masticatory function & risk of dementia

During follow-up time (median=10 years, IQR= 16-3), accounting for a total of 8638 person-years, 52 out of the 544 (9.6%) participants were diagnosed with dementia (8.6 cases per 1000 person-years). In Cox regression models with age as time scale, adjusted for sex and education, participants in Eichner categories B and C had a lower risk of developing dementia compared to Eichner A, however this was not statistically significant (**Table 3**).

Table 3. Incidence rates (IR) per 1000 person-years and HR with 95% confidence intervals (95% CI) of all-cause dementia (*n*= 52) over 22-years by Eichner categories.

Eichner Index	No. events/ person-years	IR (95% CI)	HR (95% CI)[a]	Adjusted HR (95% CI)[b]	Multi-adjusted HR (95% CI)[c]
A	13/2677	4.86 (2.82 to 8.36)	1.00	1.00	1.00
B	17/2740	6.20 (3.86 to 9.98)	0.90 (0.43 to 1.86)	0.83 (0.39 to 1.76)	1.03 (0.43 to 2.44)
C	22/3220	6.83 (4.50 to 10.38)	0.73 (0.35 to 1.50)	0.63 (0.30 to 1.29)	0.79 (0.31 to 2.03)

a Unadjusted model.

b Model adjusted for baseline sex and education.

c Additionally adjusted for birth cohort, hypertension, heart disease, periodontal disease, childhood SES, prosthesis use, and alcohol consumption.

4.2 Olfactory function & cognitive decline

4.2.1 Olfactory impairment and cognitive decline

Among the 380 participants in *Study III* (mean age = 78 ± 7 years), 138 (36.3%) had normal olfactory function, 213 (56.1%) had hyposmia, and 29 (7.6%) had anosmia. Participants with impaired odour identification (hyposmia or anosmia) were older and had lower global cognitive function. There were no significant differences in education, vascular risk factors (smoking, alcohol consumption,

and body mass index), vascular diseases (hypertension, stroke, and heart disease), diabetes, *APOE* ε4 allele, and dependency among the olfactory groups.

The mean number of follow-up assessments was 9 (±3.4) with a range from 1 to 15. Over the follow-up time, olfactory impairment, including hyposmia and anosmia, was associated with faster global cognitive decline than normal olfactory function in basic-adjusted (age, sex, and education) and multiadjusted (additionally adjusted for *APOE* ε4 and practice effects) mixed-effects models (**Figure 7**). Moreover, participants with olfactory impairment had a faster decline in episodic memory, visuospatial ability, perceptual speed, and semantic memory than those with normal function. Participants with anosmia additionally had a faster decline in working memory compared to those with normal function (**Table 4**). In stratified analysis by *APOE* ε4, the association between olfactory impairment and cognitive decline over time was present in both *APOE* ε4 carries (β = −0.07, 95% CI−0.12 to −0.02) and ε4 non-carriers (β = −0.04, 95% CI −0.06 to −0.02). There was no interaction between olfactory impairment and *APOE* ε4 on cognitive decline (β = −0.03, 95% CI −0.07 to 0.02, $p = 0.224$).

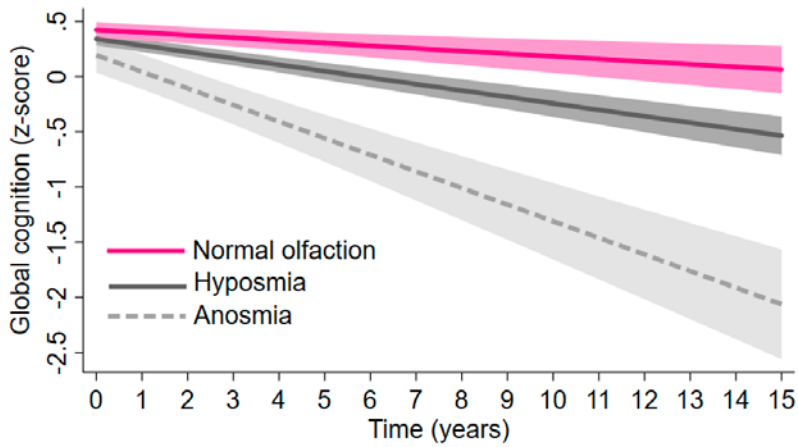

Figure 7. Predicted trajectory of global cognitive decline by olfaction categories. Model adjusted for age, sex, education, practice effects, and *APOE* ε4 allele status, with normal olfaction as reference group.

Table 4. β-coefficients and 95% confidence intervals (CIs) of olfactory function in relation to global cognition and cognitive domains

	Episodic memory	Visuospatial ability	Perceptual speed	Semantic memory	Working memory
Olfactory function	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Continuous B-SIT	0.06 (0.03 to 0.09)	0.04 (0.01 to 0.08)	0.05 (0.02 to 0.09)	0.03 (0.01 to 0.06)	0.02 (-0.01 to 0.06)
Normal olfaction	Reference	Reference	Reference	Reference	Reference
Olfactory impairment	-0.17 (-0.29 to -0.05)	-0.09 (-0.22 to 0.04)	-0.09 (-0.22 to 0.05)	-0.11 (-0.22 to 0.00)	-0.03 (-0.16 to 0.11)
Hyposmia	-0.14 (-0.26 to -0.02)	-0.07 (-0.20 to 0.07)	-0.06 (-0.20 to 0.08)	-0.11 (-0.22 to 0.00)	-0.02 (-0.20 to 0.12)
Anosmia	-0.39 -0.61 to -0.16)	-0.28 (-0.53 to -0.03)	-0.29 (-0.54 to -0.03)	-0.09 (-0.29 to 0.12)	-0.08 (-0.34 to 0.18)
Continuous B-SIT x time	0.02 (0.02 to 0.03)	0.01 (0.00 to 0.01)	0.01 (0.01 to 0.02)	0.02 (0.01 to 0.02)	0.01 (0.00 to 0.01)
Normal olfaction x time	Reference	Reference	Reference	Reference	Reference
Olfactory impairment x time	-0.06 (-0.08 to -0.03)	-0.02 (-0.03 to -0.01)	-0.03 (-0.05 to -0.01)	-0.04 (-0.06 to -0.02)	-0.02 (-0.03 to -0.00)
Hyposmia x time	-0.05 (-0.07 to -0.02)	-0.02 (-0.03 to -0.00)	-0.02 (-0.04 to -0.00)	-0.03 -0.05 to -0.01)	-0.01 (-0.03 to 0.00)
Anosmia x time	-0.13 (-0.18 to -0.09)	-0.07 (-0.10 to -0.03)	-0.10 (-0.14 to -0.06)	-0.11 (-0.15 to -0.07)	-0.05 (-0.09 to -0.02)

Models adjusted for age, sex, education, practice effects, and *APOE* ε4 allele status.

4.2.2 Trajectories of episodic memory and odour identification

In *Study IV*, the mean age at baseline was 78.2 (SD 7.5) years. The mean B-SIT and episodic memory (z-score) were 9.4 (SD 2.0) and 0.3 (SD 0.6) at baseline, respectively. The median number of assessments was 8 (IQR=8-5).

The trajectories of B-SIT and episodic memory were clearly related, as shown by the positive correlation between their random slopes (1-class model; r= 0.57, $p < 0.001$). The joint trajectories mean of the entire sample is depicted in **Figure 8A**. The best-fitting bivariate model of episodic memory and odour identification over 8 years was a 3-class model, including a class-specific intercept variance and class-invariant slope variance. The trajectories are depicted in **Figure 8B-D**. Participants in Class 1 (690, 67.4%) exhibited joint stable average performance, those in Class 2 showed stable average episodic memory and decline in odour identification (n=231, 22.6%), and Class 3 was characterised by joint decline in both episodic memory and odour identification (n=102, 10.0%).

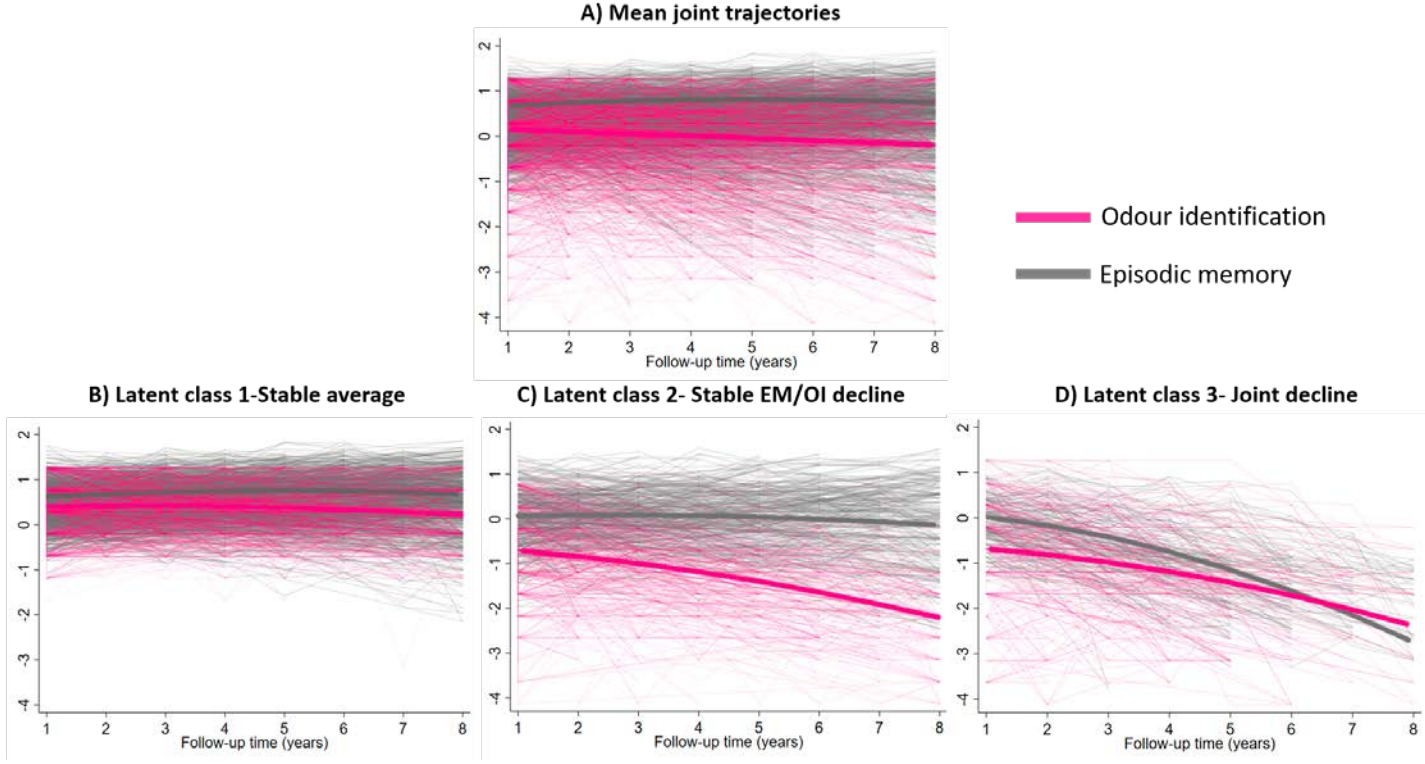

Figure 8. Fitted and observed trajectories of jointly modelled episodic memory and B-SIT scores. Scales are z-scores (mean 0, SD 1). A) The trajectories of the entire sample (*n*= 1023; B) Latent Class 1-Stable average (*n* = 690, 67.4%); C) Latent Class 2- Stable EM/OI decline (*n* = 231, 22.6%); D) Latent Class 3- Joint decline (*n* = 102,10.0%). The mean trajectories of each plot are shown in bold. EM: episodic memory; OI: odour identification.

Noteworthy is that 144 out of 690 (20.9%) subjects died in Class 1 (stable average) during follow-up, 84 out of 231 (36.4%) died in Class 2 (average episodic memory/declining odour identification), and 62 out of 102 (60.8%) participants died in Class 3 (joint decline); 59 participants (8.6%) developed dementia over follow-up in Class 1, 59 (25.5%) in Class 2 and 69 (67.7%) in Class 3; participants in Class 1 were younger than those in Class 2 or 3, however the latter two classes did not differ significantly in age.

4.2.3 Predictors of trajectories in episodic memory and odour identification

Further, we investigated which factors could predict joint class membership of the three patterns (joint stable, declining odour identification, and joint decline). Compared to the stable Class 1, people in Class 2 were more likely to be older (OR: 1.11, 95% CI: 1.08 to 1.14) and male (OR: 1.98, 95% CI: 1.33 to 2.95). People in the joint declining Class 3 were more likely to be older (OR: 1.15, 95% CI: 1.10 to 1.20), *APOE* ε4 carriers (OR: 2.66, 95% CI: 1.57 to 4.52), have a lower BMI (OR: 0.93, 95% CI: 0.88 to 0.98), and be less engaged in cognitive activities (OR: 0.62, 95% CI: 0.43 to 0.89).

4.3 Dental health & brain volume differences

In multiadjusted linear regression analyses, participants with complete tooth loss had significantly lower TBV (β: -52.70, 95% CI: -8.79 to -16.61) compared with the no tooth loss group. In addition, significantly lower GMV was observed among the partial (β: -17.10, 95% CI: -33.54 to -0.67) and complete tooth loss group (β: -36.77,95% CI: -62.78 to -10.77) compared with the no tooth loss group. A lower HV was observed in those with tooth loss compared to those with no tooth loss; however, this association did not reach significance likely due to lack of power. There was no significant association between tooth loss and WMV or volumes of WMHs (**Figure 9**). After removing incident dementia cases in the MRI subsample (*n*= 37), the association between tooth loss and GMV remained significant (β =-44.56, 95% CI: -81.33 to -5.78).

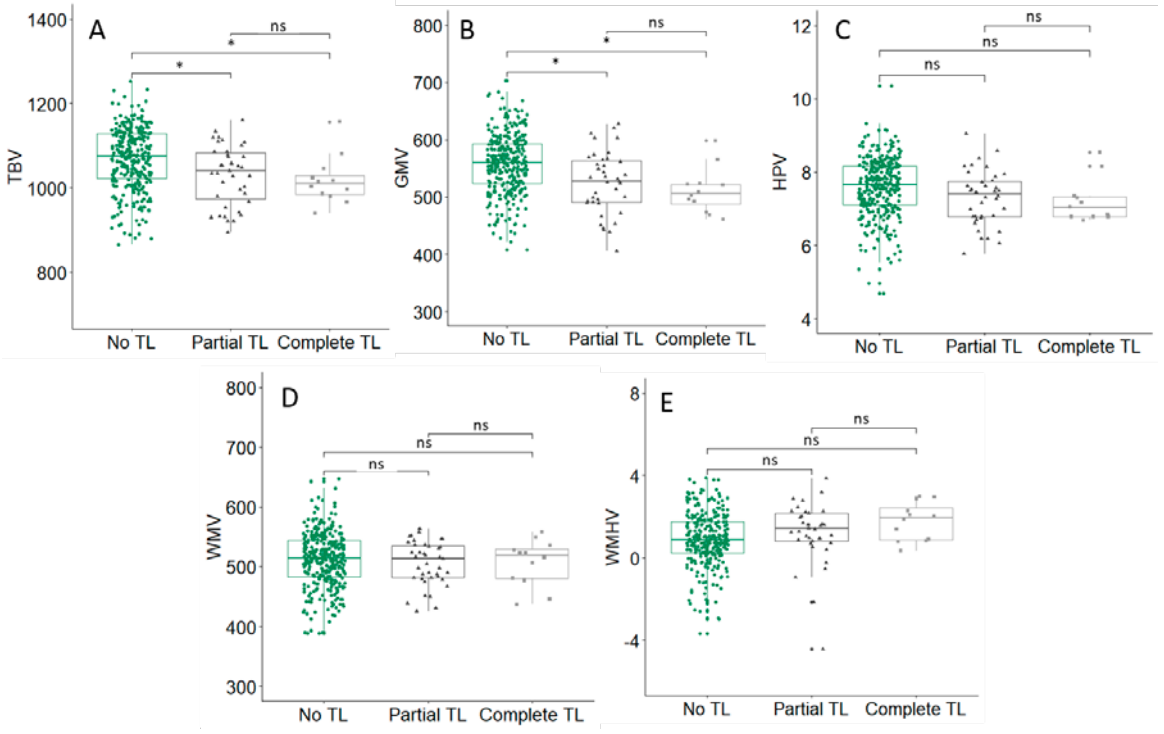

Figure 9. (A) Total brain volume (TBV), (B) Grey matter volume (GMV), (C) Hippocampal volume (HV), (D) White matter volume (WMV), (E) White matter hyperintensity volume (WMHV). Box plots represent the means and standard deviations in n=394 SNAC-K participants. All volumes were adjusted for total intracranial volume and age. *Significant group differences derived from linear regression models with tooth loss as categorical predictor variable (reference group: no tooth loss) and regional brain volumes as continuous outcome variables, respectively. Models were adjusted for sex, education, cardiovascular diseases, C-reactive protein, multimorbidity, *APOE* ε4 allele and baseline MMSE score.

4.4 Olfactory function & brain volume differences

In *Study III*, a higher B-SIT score was associated with greater volumes of the hippocampus, ERC, amygdala, fusiform gyrus, temporal pole, and inferior temporal cortex (**Table 5, Model 1**). Moreover, participants with olfactory impairment had lower volumes in the hippocampus, ERC, middle temporal cortex, and fusiform gyrus compared to those with normal olfactory function (**Figure 10**). The association between olfactory impairment and volumes in the hippocampus, ERC, fusiform gyrus, and middle temporal cortex remained significant after excluding participants diagnosed with dementia during the follow-up of the study.

Table 5. β-coefficients and 95% confidence intervals (CIs) of olfactory function (continuous B-SIT) in relation to regional brain volumes using linear regression.

Regional brain volumes	**Model 1*** β (95% CI)	**Model 2*** β (95% CI)
Hippocampus	0.05 (0.02 to 0.08)	0.04 (0.01 to 0.08)
Entorhinal cortex	0.04 (0.02 to 0.06)	0.03 (0.01 to 0.05)
Amygdala	0.02 (0.01 to 0.03)	0.02 (0.00 to 0.03)
Inferior temporal	0.15 (0.05 to 0.24)	0.11 (0.01 to 0.21)
Fusiform	0.12 (0.04 to 0.20)	0.11 (0.02 to 0.19)
Temporal pole	0.03 (0.00 to 0.06)	0.03 (-0.01 to 0.05)
Middle temporal	0.11 (0.02 to 0.20)	0.07 (-0.02 to 0.17)

Regional brain volumes are expressed as tenths of percentages of ICV.

* Model 1 adjusted for age, sex and education, and Model 2 adjusted for age, sex, education, *APOE* ε4 status, baseline global cognition and scanning site.

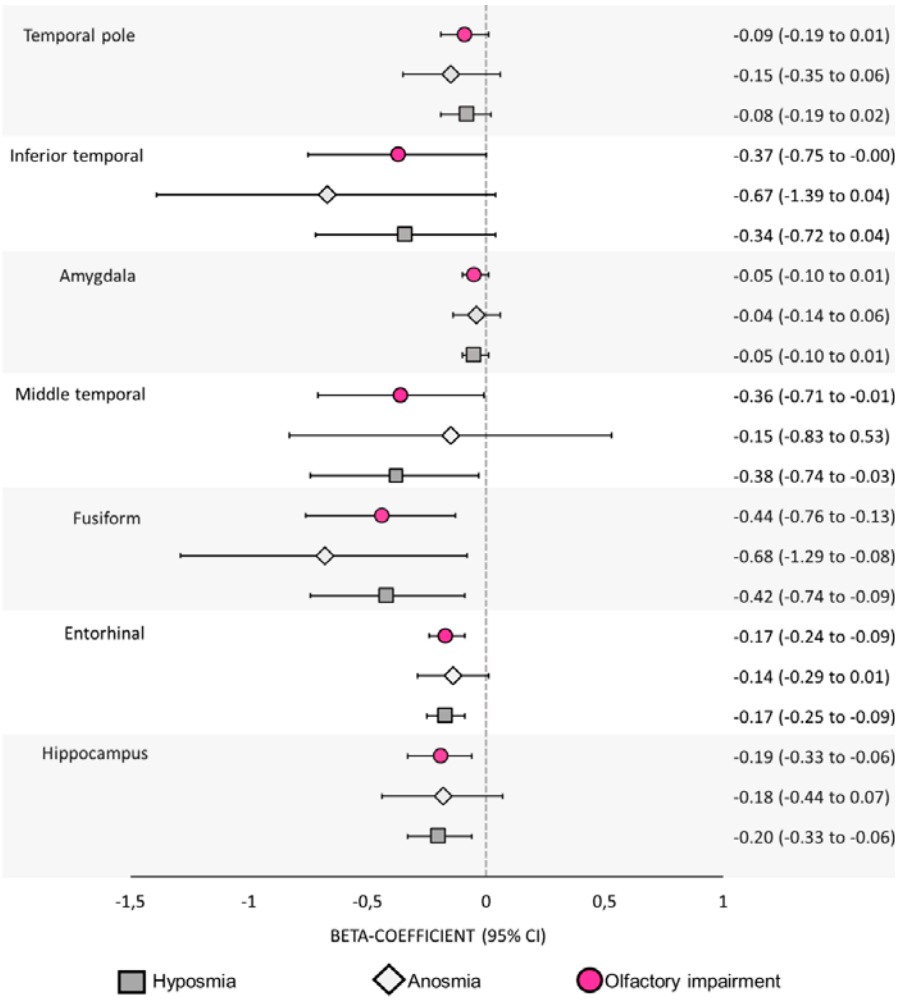

Figure 10. β Coefficients and 95% CIs of olfactory function in relation to regional brain volumes from linear regression (adjusted for age, sex, education, *APOE* ε4, baseline global cognition, and scanning site). Olfaction categories were defined based on baseline Brief Smell Identification Test scores as follows: anosmia (score <6), hyposmia (6–10 men, women 6–10.25), and normal olfaction (10.25–12 men, women 10.5–12). Volumes are expressed as tenths of percentages of intracranial volume. CI = confidence interval.

4.5 Summary of cognitive trajectories according to oral health measures and olfactory function

Figure 11 depicts the cognitive trajectories measured with MMSE, according to tooth loss status in *Study I* (SNAC-K), Eichner categorisation in *Study II* (SATSA), and olfactory function in *Study III* (MAP). In these analyses, age was used as time-scale due to different lengths of follow-up time among the datasets. The same inclusion criteria were used, excluding only prevalent dementia cases and controlling for factors specific to the respective exposures as previously described. The average decline in MMSE over a ten-year period for individuals with partial tooth loss was 1.2 points (95% CI: 2.0 to 0.4) and 2.5 (95 % CI: 3.9 to 1.1) for those with complete tooth loss, compared to having no tooth loss. Compared to individuals in Eichner category A, those in category B declined 1.2 points (95% CI: 1.9 to 0.4), while those in category C declined 1.7 points (95% CI: 2.4 to 1.0) . Decline in MMSE was on average 2.3 points (95% CI: 3.1 to 1.5) in people with hyposmia, and 3.3 points (95% CI: 4.6 to 2.0) in those with anosmia, compared to individuals with normal olfaction.

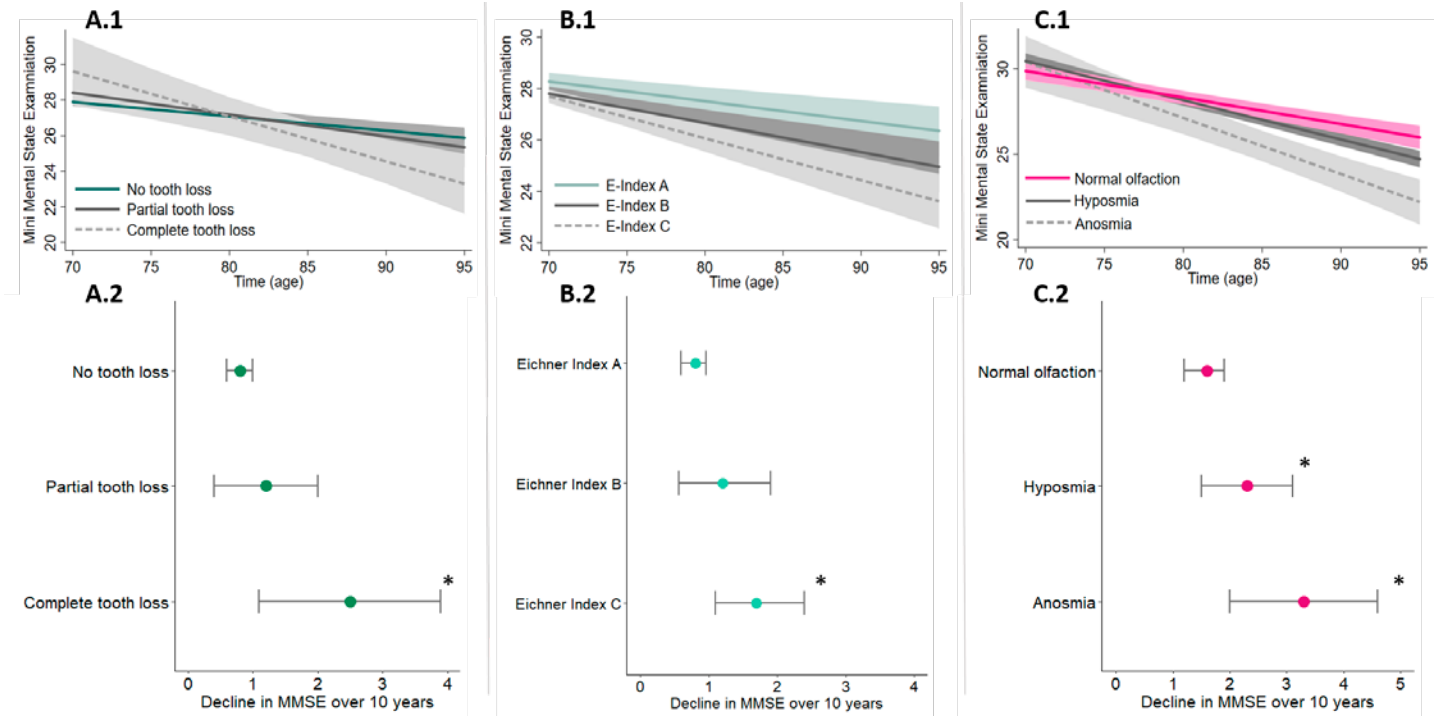

Figure 11. MMSE trajectories according to oral health measures and olfactory function. Mixed-effects models using age as time scale, excluding prevalent dementia and missing on exposure, and adjusting for exposure specific covariates. A.1) MMSE trajectories (*n*=2715, SNAC-K) by tooth loss status; A.2) average MMSE decline over 10 years by tooth loss status, reference: No tooth loss; B.1) MMSE trajectories (*n*=582, SATSA) by Eichner Index categories; B2) average MMSE decline over 10 years by Eichner Index categories, reference: Eichner A; C.1) MMSE trajectories (*n*=380, MAP) by olfactory function categories; C.1) average MMSE decline over 10 years by olfactory function categories, reference: Normal olfaction.

5 DISCUSSION

5.1 Summary of main findings

This doctoral project investigated the impact of oral health and olfactory function on cognitive- and brain ageing, using data from three population-based longitudinal studies. The main findings from *Study I* showed that tooth loss was associated with accelerated cognitive decline over 9 years, especially in those with complete tooth loss. This association remained after controlling for several indicators of health status, functionality, and lifestyle. Moreover, tooth loss was cross-sectionally associated with smaller TBV and GMV. In *Study II*, sub-optimal mastication indicated by Eichner Index B or C was related to a faster decline in spatial/fluid abilities in cognitively intact older adults. In *Study III,* olfactory impairment was related to an accelerated cognitive decline, most prominently in episodic memory, as well as lower volumes in the hippocampus, entorhinal, fusiform and middle temporal cortices. In *Study IV*, episodic memory and odour identification showed similar patterns of trajectories over time and could be predicted by baseline age, sex, BMI, cognitive activity, and *APOE* ε4 status.

5.2 Oral health & cognitive decline

Recently, a number of systematic reviews and meta analyses from Western and Asian countries have examined the link between oral health measures and cognitive status [80,187–189]. Wu et al., included studies using various oral health measures as exposures (tooth loss, periodontitis and caries, and use of denture) in relation to cognition, most frequently assessed with the MMSE, or dementia diagnosis. The authors found that tooth loss and periodontal disease were associated with accelerated cognitive decline or an increased risk of dementia, while others did not find such associations [187]. Tonsekar et al., examined the effects of chronic periodontitis and tooth loss as assessed by oral examination and radiographic images, on cognition measured with different cognitive tests/dementia diagnosis [188]. Out of the studies with measures of tooth loss, 4 out of 8 reported an association between multiple tooth loss and lower cognitive scores. One study found that edentulism in late-middle-age was associated with lower cognitive level, however, it was not associated with subsequent cognitive impairment [190]. Conversely, a prospective longitudinal study from France reported that tooth loss of more than 11 teeth was associated with a lower risk of dementia in participants with lower education [191]. Moreover, the meta-analysis by Shen et al. included cohort studies, cross-sectional studies, and case-control studies, concluding that tooth loss is a risk factor for dementia [189]. However, due to the inclusion of cross-sectional and case-control designs, the temporality of the associations is questionable. Lastly, Oh et al., assessed the relationship specifically between the

number of residual teeth and the risk of dementia [80]. Compared to having a low number of remaining teeth, having a high remaining number of teeth reduced the risk of dementia by approximately 50%. The authors however, graded the overall quality of evidence as very low [80].

The conclusions from these meta-analyses have been either that the evidence is inconclusive, or points to poor oral health being a risk factor for cognitive impairment, despite limited scientific strength. These discrepancies might be due to several reasons, such as differences in the age and sociodemographic characteristics of the study populations, and inclusion of people with preclinical dementia or cognitive impairment. One of the main reasons as to why it is difficult to corroborate evidence regarding the effect of oral health on cognition, is due to that it encompasses several aspects, conditions and diseases. Moreover, different markers of oral health may be related to adverse health consequences, including cognition, through different pathways.

In *Study I*, we found that tooth loss was associated with a steeper cognitive decline and lower GMV. In this study, we attempted to address several of the weaknesses from previous studies through the prospective design, controlling for functional and health measures, lifestyle factors, as well as genetic and inflammatory factors. In sensitivity analyses, we excluded participants with incident dementia, which showed similar, albeit non-significant results, likely due to loss of power. Moreover, the inclusion of MRI measures of WMV and GMV, provided a neurobiological dimension in support of the behavioural findings, which remained after excluding incident dementia cases in the MRI sample.

While tooth loss has been used most frequently as a marker of oral health, it is possible that some long-term adaptation to the edentulousness/tooth-loss condition in mastication is possible. Therefore, although being practical and reliable, the number of teeth lost per se may not fully reflect masticatory function. Using self-reported masticatory ability as an exposure of interest, a cross-sectional Swedish study of older community dwelling people showed that participants with difficulty in chewing hard food such as apples had a lower cognitive performance [192]. The authors also found that whether or not the dentition was natural or prosthetic had no significant influence on the observed association. This was indeed supported by our findings from *Study II*, whereby having more posterior contacts was associated with better cognitive abilities in older Swedish adults over up to 22 years.

Some studies have focused on occlusal contacts as a measure of masticatory ability, which has been shown to correspond to functional assessments of mastication [193]. A study with cognitively normal older Dutch persons, revealed that 19% of the variation in episodic memory function could be predicted by jaw mobility and bite strength and that 22% of the variation in executive function was related to

self-reported complaints about masticatory function [81]. Another study showed that word recall, verbal fluency, and numeracy was significantly better in people with good chewing ability, functionally measured with a two-colour gum mixing ability test [194]. *In Study II*, we found baseline associations between Eichner categories and verbal ability, however, we found no effects of masticatory ability on trajectories of change in verbal ability. Verbal ability at any one moment could be affected by mobility problems of the jaw as well as pronunciation difficulties due to more recent tooth loss, rather than a manifestation of neural abnormalities related to poor oral health [196]. Similarly, we did not find an association between masticatory function and memory, as two previous cross-sectional studies have shown [81,197]. The reason for this could be reverse causality due to pre-clinical cognitive impairment or dementia [198], which can lead to poorer oral health care. In *Study II*, we excluded participants with CIND at baseline, thereby reducing the chances of reverse causality.

Thus far, only two studies examined the relationship between masticatory and cognitive function or dementia longitudinally. One study reported a steeper decline in those with fewer posterior occlusal pairs [102]. However, cognitive function was measured using the Japanese version of the Montreal Cognitive Assessment, and therefore there was no indication of the longitudinal effects of masticatory function on specific cognitive domains, which could elucidate potential mechanisms involved. In the present study, we found an association between occlusal support and spatial/fluid ability. This is in line with a cross-sectional study showing that poorer mastication is related to worse executive functioning as well as reduced cerebral blood flow to the pre-frontal cortex, responsible for higher order cognitive processes [199].

To the best of our knowledge, *Study II* is the first prospective study that has investigated the association between an objective measure of mastication and the risk of dementia. We did not find poorer masticatory ability to be associated with a higher risk of dementia. This is in line with another study showing no increased risk of dementia over 4 years in participants with poorer self-reported mastication [101]. However, on average, participants with Eichner C were 10 years older than those in category A, were overall in worse health, and had the highest proportions of death during the study period. Therefore, while masticatory function could accelerate cognitive decline, due to the likely competing risk of death, those with the poorest masticatory function may not live long enough to develop clinical manifestations of dementia.

5.3 Mechanisms underlying oral health & cognition

The biological mechanisms behind the association between oral health and accelerated cognitive decline are not well understood; however, several hypotheses have been put forward.

Inflammation. Periodontitis, one of the most common causes of tooth loss [206], is related to elevated inflammation [200,201], which has been implicated in the pathogenesis of dementia [202–204], such as higher brain amyloid load in cognitively normal older adults [205]. Chronic periodontitis may act as a peripheral source of systemic inflammation, exacerbating the neuropathological processes of dementia [76, 207–214]. In *Study* I, controlling for inflammatory status attenuated the association between tooth loss and cognitive decline. However, while CRP is a sensitive marker of systemic inflammation, it is not specific to inflammatory processes in the oral cavity and is more a marker of acute- rather than chronic states of inflammation. Future studies with markers of chronic inflammation should further investigate the timing between tooth loss, inflammatory response, and cognitive outcomes.

Vascular diseases. CVDs have been proposed to play a role in the relationship between poor dental health and cognitive decline. Several studies have reported a higher risk of CVDs and cerebrovascular disease in persons with poor dental health [88–91]. Findings from *Study I* indicate that the effect of tooth loss on cognitive decline was not explained by cardio- and cerebrovascular diseases. However, since this link may be stronger in participants who have long history of periodontal disease, and as we did not have information on the cause of tooth loss, the interpretation of the role of vascular diseases in *Study I* may be limited.

SES. The role of SES is important to consider in relation to oral health. Parental SES could be associated with worse dental care in childhood and financial difficulties, reducing the access to dental care. In *Studies I* and *II*, controlling for SES factors such as education, occupational status, and childhood SES, did not modify the relationship between oral health markers and cognitive decline. Nevertheless, future studies with larger samples further investigating the role of SES in the relationship between oral health and cognitive decline, are warranted.

Neurodegeneration. Findings from animal research suggest that experimentally induced edentulism is associated with neurodegeneration and reduced neurogenesis, particularly in the hippocampus [93–96] and widespread brain morphological changes [92]. *Study I* was the first to show structural brain differences in relation to tooth loss in humans. Indeed, we found that dementia-free participants with tooth loss had lower TBV, and GMV in particular. Additionally, participants with complete tooth loss tended to have lower HV compared with the no tooth loss

group, albeit not a significant difference. A recent study with a small sample of dementia-free participants from a dental clinic, showed that edentulous individuals had lower volumes in the hippocampus, caudate nucleus and temporal pole [215]. These areas are important for learning and memory, echoing findings from animal studies [93–96]. Taken together, these findings indicate that poor dental health may be a risk factor for neurodegeneration in dementia-free older adults; however, these exploratory cross-sectional findings need to be validated in future longitudinal neuroimaging studies.

Nutrition. Poor oral health could impact cognition through modifying nutritional intake. However, evidence on the role of nutrition in the relationship between oral health and cognition is limited. In one study, authors reported an increased risk of dementia in catholic nuns followed for 21 years. This was a homogenous group, with similar diet and lifestyle [216]. Moreover, one study found that tooth loss was significantly associated with dementia, and tooth loss was also associated with poorer nutritional status; however, this did not explain the association with dementia [217]. A cross-sectional study conducted path analysis confirming the hypothesis that cognitive function was associated with occlusal force directly as well as indirectly via food intake [218]. We addressed this in *Study I* by adjusting for markers of poor nutrition, which did not modify the results. Future longitudinal studies with detailed dietary indices should further investigate the role of nutrition in the link between oral health and cognitive ageing.

Sensory stimulation. Another possible pathway between oral health, cognitive decline, and brain morphological changes, may be through reduced sensory stimulation caused by poor masticatory ability. Experimental models of edentulism show reduced masticatory-induced sensory stimulation, as well as brain changes in cortical regions involved in somatosensory, motor, cognitive, and emotional processing [92–96]. In humans, functional MRI studies have shown that during chewing, there is increased brain activity in the prefrontal cortex, anterior cingulate cortex, and left frontal gyrus [199,219]. Furthermore, masticatory ability has been positively related to GMV and resting-state functional connectivity in the dorsolateral prefrontal cortex [220]. The lower GMV observed in participants with tooth loss in *Study I*, is in support of these findings.

Moreover, there is evidence of possible circularity, in that loss of attachment and injury to the dental root causes loss of important feedback via the CNS, leading to reduced control and efficiency of processes such as mastication [221–227]. Such loss of integrity of the oral cavity encompasses a reduction in afferent nerve stimulation, which may cause sensory and motor cortical reorganisation [228–230], affect cerebral functional streams toward multisensory hubs [231,232], and result in memory and cognitive impairment [20]. This may also be reflected in decreases in

cerebral blood flow, particularly to the frontal cortex in individuals with impaired masticatory ability [233,234].

In summary, poor oral health may negatively affect the brain by a) being a source of chronic inflammation, thereby exacerbating neuropathological processes, and b) sub-optimal mastication reducing feedback to the frontal cortex, affecting higher order cognitive functions.

5.4 Olfaction & cognitive decline

Several population-based studies have found that poorer olfactory performance is associated with cognitive decline [120,122,123,128,235]; however, most of these studies had short follow-up time. One prospective study with up to 16 years of follow-up found no evidence of an association between odour identification performance and cognitive decline [147]. A possible reason for such mixed findings could in part be related to the failure of taking into account the effects of preclinical dementia [120], considering that the influence of dementia pathology on cognition may begin several years before a clinical diagnosis. Another study showed that the pattern of global cognitive decline related to olfactory deficits was similar before and after excluding dementia cases (dementia diagnosed up to 5 years after baseline) [120].

Previous reports from studies with the MAP population showed that poorer olfactory performance was associated with faster cognitive decline and AD pathology [107,169,236]. In *Study III*, we built on these findings by including to 15 years of follow-up and cross-sectional structural brain MRI measures. We confirmed that olfactory impairment was associated with an accelerated global cognitive decline over 15 years, which persisted after excluding all incident dementia cases over the follow-up time. Previous work from the using the MAP population has shown a faster decline in perceptual speed and episodic memory [236]. In *Study III*, with longer follow-up time, impaired olfactory function was additionally associated with faster decline in visuospatial memory and semantic memory. Studies using the SATSA population showed an association between odour identification and several measures of verbal ability [237]. This is in line with our results, wherein the semantic memory composite included measures of verbal ability (see **Appendix Table 1**) [124]. However, only the association with episodic memory remained significant after removing incident dementia cases in *Study III*. This indicates that impaired olfactory function could be a predictor of subsequent cognitive impairment independent of pre-clinical dementia.

Atrophy in the primary olfactory cortex (ERC and amygdala) has been found in previous studies in young adults with anosmia and hyposmia [175, 143]. Atrophy in the primary olfactory cortex has also been reported in cognitively normal older

adults with olfactory impairment [108, 239], as well as lower activity in this area during olfactory tasks [109]. In accordance with these studies, we found that olfactory impairment was associated with lower volume in the fusiform gyrus and the middle temporal cortex (including the hippocampus and ERC). These findings suggest that olfactory impairment is associated with AD signature areas in dementia-free older adults.

Previous studies reported a faster decline in cognitive performance exclusively in or most pronounced, in *APOE* ε4 carriers with olfactory impairment [149,240,241]. Moreover, evidence from studies recording event-related potentials (ERP) showed that non-demented ε4 carriers display greater effort in odour recognition tasks or engage in compensatory strategies, requiring more brain activation or recruitment of alternative brain areas [242,243]. In *Study III*, we did not find an interaction between *APOE* ε4 allele status and olfactory impairment on cognitive decline. The decline tended to be steeper in ε4 carriers, however it was not significant, likely due to limited statistical power.

In *Study IV*, we identified three patterns of joint trajectories in odour identification and episodic memory. In two out of the three joint trajectories identified (stable Class 1 and declining Class 3), odour identification and episodic memory progressed in parallel. This is in line with evidence showing a close overlap of olfaction and episodic memory areas in the middle temporal cortex, and would suggest that these two processes indicate the integrity of such brain structures [246,247]. Interestingly, in Class 2, episodic memory had a stable average trajectory, whereas odour identification was steadily declining. This may seem contrary to the patterns observed in the other two classes. However, compared to memory structures, the olfactory system has been shown to be especially sensitive to non-dementia related pathology, and environmental agents [103]. Olfactory decline is quite common in old age, and such decline may be caused by a wide variety of factors, including accumulated environmental damage to the olfactory epithelium, changes in nasal airflow and mucus composition, or declining sensitivity and tuning of receptor neurons, all of which would contribute to poor or declining olfactory performance [248,249]. We therefore speculate that Class 2, characterised by declining odour identification but retained memory ability, is to a large extent made up of individuals with peripheral olfactory dysfunction.

Furthermore, we found that odour identification and episodic memory were correlated over time, showing similar trajectories in *Study IV*. Our findings are compatible with those of a recent study, which showed that episodic memory scores and B-SIT scores fluctuate together over measurement occasions, using B-SIT scores as a time-varying covariate when modelling episodic memory decline [149]. The authors of the previous study also reported that there was a stronger positive

relationship between B-SIT and episodic memory fluctuations for individuals with intermediate to high AD pathology. The evidence thus points to AD pathology as a mediator in the decline in both behavioural domains. Indeed, in *Study IV*, we found that being an *APOE* ε4 carrier, a known risk factor for AD [250], increased the likelihood of belonging to the "concurrent decline" Class by almost 3-fold. A previous study found that episodic memory decline was associated with odour identification impairment only in ε4-carriers, suggesting that the ε4 is involved in the functional association between ongoing episodic memory decline and olfactory function [146]. In a study investigating "change-change" correlation in episodic memory and odour identification, the correlation was only seen in *APOE* ε4 carries, specifically ε4 homozygotes [149]. The findings from *Study IV* support the notion that ε4-carriers, compared to non-carriers, display a cortical atrophy pattern that is more focused on medial temporal lobe regions supporting olfactory and episodic memory functions [151].

In addition, we found that age, sex, BMI, and cognitive activity were predictors of joint trajectories of odour identification and episodic memory. The findings related to older age are consistent with previous studies showing that both odour identification and episodic memory decline with increasing age [103,251]. Male sex has been associated with lower olfactory performance in previous studies [252], and was also a predictor of Class 2 membership in the current study. Higher BMI was associated with lower probability of belonging to Class 3, which is in line with an emerging body of work reporting high BMI appearing to be protective of dementia due to weight loss in pre-clinical stages [253], as this class had the highest number of individuals who were diagnosed with dementia over follow-up. Lastly, a low engagement in cognitive activities predicted joint class membership. Such activities are postulated to be protective against dementia and to delay the clinical manifestation of AD pathology as "resilience" factors [254–256]. In the joint declining Class 3, cognitive activity at baseline was relatively lower, which may partly explain the steep joint decline. However, whether or not the decline in cognitive activity contributed to cognitive decline or may be a reflection of it, cannot be determined in this study.

5.5 Mechanisms underlying olfactory function & cognition

Common cause. Sensory and cognitive deficits have been suggested to reflect a "common cause", such as AD pathology or neuronal injury [6, 121, 127, 257]. Sensory impairments likely may predict cognitive impairment for different reasons. Some may reflect the "common cause" hypothesis, i.e. impairment due to common effects of pathology or ageing-related processes, while others may reflect the "sensory deprivation" hypothesis; whereby impairment leads to a loss

of perceptual input, negatively impacting the brain. Yet, these hypotheses are not mutually exclusive. For example, hearing impairment has been declared as a possible mid-life risk factor for dementia, possibly due to disengagement or due central auditory areas being vulnerable to by AD pathology [54]. On the other hand, central hearing loss that is followed by AD is rare, at 2% of the older population [258]. Conversely, there is convincing evidence of involvement of shared neuropathology relating olfactory and cognitive impairment [107,143,144], reflected in the findings of *Study IV*. Hence, olfactory impairment may present higher diagnostic value for clinical outcomes related to such neuropathological changes.

Neuropathology. It has been suggested that olfactory impairment in old age may be a reflection of neuropathology specific to ageing processes rather than AD. A previous study with the MAP study population found that tangle density within areas of the central olfactory system (e.g. ERC) was strongly related to odour identification test scores, whereas tangle density in areas outside the system was not, indicating that neurofibrillary pathology is a contributing factor of impairment in odour identification in old age [107]. In this vein, a recent study showed that odour identification scores were negatively correlated with concentrations of t-tau in CSF [144]; however, there was no significant association between cerebrospinal markers of amyloid plaque. The authors concluded that odour identification impairment may be an indicator of neuronal injury rather than amyloid pathology, echoing results from other imaging studies showing no relationship between olfactory impairments and amyloid deposition [259,260] Moreover, hippocampal atrophy has most often been used as a neurodegenerative marker of AD [261]; however, it is not specific for this disease and could be an indicator of neurodegeneration caused by other ageing-related processes, including tauopathy [262]. This is indeed also the case for the amygdala, in which age-related reductions in volume have frequently been reported [104,263].

***APOE* ε4.** It has also been suggested that effects of *APOE* ε4 on olfactory function performance could be independent and in parallel of its association with AD pathological processes [248, 264]. For normal olfactory processing, it requires continuous cellular regeneration throughout the human life span. The *APOE* ε4 allele has been shown to impair the process of neuronal differentiation and neurite outgrowth in the olfactory epithelium [145]. Hence, carries of the ε4 allele may be at higher risk of olfactory impairment independently of their risk to develop dementia. However, this does not exclude the possibility of that the interaction between *APOE* ε4 and olfactory function reported in previous studies, may reflect pre-clinical AD pathology. This is in contrast to findings regarding the association between episodic memory and *APOE* ε4 carrier status, whereby steeper decline in episodic memory in ε4 carries, has largely been attributed to the presence of pre-clinical dementia [181].

Inflammation. The nasal cavity is susceptible to, and may provide a pathway for infections triggering the release of inflammatory mediators which can enter the CNS. Similarly to how tooth loss may be a marker of past or present inflammatory response, olfactory impairment may also reflect an underlying inflammatory condition or an inability to clear pathogenic bacteria from the sinonasal cavity. The prevalence of conditions known to impair olfactory perception such as rhinosinusitis and sinusitis increase with age and may be such source of systemic inflammation [265,266]. This inflammatory hypothesis in relation to the link between olfactory impairment and cognitive decline was not a focus of this thesis, however, it represents a potential avenue for future research.

It should be noted that it is likely impossible to completely differentiate memory processes from olfactory perception, since memory is engaged in most psychophysical olfactory tests and consciousness itself can be regarded as a form of memory [267]. Although the memory and language component in the B-SIT is minimised due to multiple-choice options facilitating cueing, the impaired B-SIT scores may also result from pre-clinical memory dysfunction. However, previous studies have shown that the association between olfactory identification and AD-neuropathology was not moderated by variations in semantic memory [107,144], suggesting that the association between odour identification and cognitive decline and dementia is independent of the level of semantic memory or vocabulary [126].

In summary, olfactory function and cognition, in particular episodic memory may be strongly related because a) they both rely on structures in the medial temporal lobes, and are therefore vulnerable to neuropathology and atrophy in these regions, and b) the *APOE* ε4 allele has influence on both olfactory function and episodic memory.

5.6 A note on predictors and risk factors

Epidemiological research in public health is conducted for two main reasons, a) risk stratification or prediction, and b) assessing causality. These are in essence two separate questions and aims, i.e. prediction versus explanation, involving different methods, resulting in different interpretations. Nevertheless, factors that do not predict risk are seldom classified as causal factors (for example ubiquitous factors in a population) [268]. The aim with prediction is to identify individuals or groups with higher risk of a particular health condition (the causal structure not inferred), in order to provide appropriate interventions.

Explanatory models are designed to assess whether a particular “risk factor” explains the occurrence, or course, of disease, and as such is a valid target of intervention [269]. A considered predictor of a condition is not per se a valid target for

intervention. Taking the example of influenza, the flu symptoms do not cause the condition, and therefore are not targets of preventative measures in flu prevention. In order for the proposed risk factor to be considered a target of intervention, it has to be established from different studies designed to test the causal structure. Moreover, observational studies designed to assess causal structures are especially vulnerable to sources of bias, the main sources being confounding and selection bias [270], discussed in more detail in 5.7.2.

There is a fair amount of ambiguity in causative research terminology. When differentiating between causal associations and non-causal associations, the term risk factor often is used indiscriminately for all factors associated with the outcome, whether a causal relationship is assumed or not. However, the term risk factor should be used with caution, when a causal relationship is reasonably established. The non-casually associated factors, which may indicate a disease or outcome, can be referred to as risk indicators, risk determinant, or predictor depending on the context [270].

In the case of olfactory function, the approach of analysis and interpretation has been to regard olfactory impairment as a predictor of cognitive decline and brain morphology. This perspective was based on past literature and evidence, which has mostly held the position of a non-causative role of olfactory impairment in future cognitive decline and dementia, despite performing well as a predictor. The findings from this thesis supports the general consensus that impaired odour identification could predict insipient cognitive impairment. On the other hand, olfactory impairment as mentioned previously can be a marker of peripheral inflammatory processes which arise in the nasal cavity and reaches the CNS, or a marker of neuropathology; therefore, it could it could be argued that olfactory impairment is a risk indicator. Moreover, in *Study IV*, we identified a group of individuals who declined only on odour identification, while remaining stable in episodic memory over 8 years. This group had similar baseline levels as the group who declined in both function. Therefore, if odour identification should be used in the clinic in cognitive assessments or prognosis of decline, it is relevant to understand the aetiology of the odour impairment, as was shown from the determinants in each class in *Study IV*.

Oral health was considered a possible risk factor for accelerated cognitive decline and dementia, based on findings mainly from animal studies indicating a causal relationship, as well as human studies, albeit with limited evidence quality. The findings from this thesis, support the hypothesis that poor oral health may be a risk factor for cognitive impairment and dementia, after controlling for multiple possible confounding factors. However, if one considers the definitions above, the causal mechanisms for this relationship are not understood well enough for it

to be considered established. Hence, tooth loss per example, may be a risk indicator due to its association to another factor which we were not able to adequately account for in these studies. An example of such a factor could be periodontal disease. Moreover, oral health served quite well as predictor of decline in general cognition and specifically fluid/spatial ability; hence, whether or not the mechanisms are well understood, oral health seems to be a good predictive factor that could be used to identify persons at risk for cognitive impairment, for example in dental health care contexts.

5.7 Methodological considerations

Researchers in cognitive ageing or interested in any late-life outcomes, will face several methodological issues because of the fact that the study population in question is ageing. Some of the consequences of which, may or may not be the subject of study. Such consequences include poor health and physical and cognitive impairments. This could cause data collection from older participants, whether cross-sectional or longitudinal, to suffer from low response rates. In particular, this is challenging because such selection may not be random. Apart from affecting response-rate, such differences can moreover lead to selective mortality with the risk of biasing findings. Therefore, it is important to consider missing data and different sources of bias when interpreting the results of observational studies involving older adults.

5.7.1 Misclassification

Some challenges are related to how the exposures, outcomes and covariates are assessed. The challenge is to use measures which reflect the exposure and outcome of interest and ideally to avoid residual confounding. It is a balance between using optimal measures and to make studies comparable to other studies in the same field. In the case of oral health, the types of assessments vary widely between studies and may sometimes depend on availability of measures and research aim.

In *Study I*, we used self-reported tooth loss as a measure, based on categorisation from previous work using the SNAC-K population and by consultation with I. Wårdh (DDS, specialist in Orofacial medicine). The categorisation was made by grouping statements related to participants' dental status. In sensitivity analyses, we used the original variable with each possible answer as exposure in the models for cognitive decline and found that the patterns of cognitive trajectories reflected well the categorisation we had specified.

The problem with self-reported data in general, is that you have to rely on that the participants' answers are valid and reliable. However, in the case of dental health,

making the correct judgment on their status requires that the participants are cognitively intact enough to be able to understand the question and its alternatives, and correctly identify which alternative is the best representation of their status. We excluded participants who had clinically established dementia and those with questionable dementia at baseline; however, sub-clinical cognitive decrements may have affected the quality of the self-reported dental status, creating so-called differential misclassification [271]. When removing all incident dementia cases over the follow-up, the proportions in the three categories remained almost identical, indicating that the effects of preclinical dementia on the self-report was minimal. Moreover, misclassification could occur ubiquitously in the sample, due to reasons such as misunderstanding the question or alternatives, or unwillingness to give a true answer, which should be non-differential [272].

In SATSA, the status of each tooth (**Appendix Figure 1**) was assessed by a nurse. The Eichner categorisation was based on this objective assessment. Misclassification could have occurred due to inaccurate categorisation. A random 10% of the participant categorisation was checked by I. Wårdh; 1 participant was misclassified, indicating 0.02% non-differential misclassification, which usually biases towards the null.

Interestingly, the proportion of edentulous participants with or without dentures in SNAC-K and SATSA, differed greatly with 7.6% and 25.7%, respectively. This may reflect either misclassification in SNAC-K due to self-report, or cohort effects in dental care as the baseline assessments differed by a decade, or SES differences considering the SNAC-K participants are majority white collar.

In *Studies III* and *IV*, the B-SIT was used as a measure of odour identification. Differential misclassification could occur if participants due to pre-clinical dementia, are not able to identify the correct odour. Moreover, inability to identify an odour could be due to other reasons such as a cold or seasonal allergies, or unfamiliarity with a particular odour, which should be non-differential.

In *Studies II, III,* and *IV*, cognitive function was measured with composite scores from neuropsychological tests. Composite scores have the advantage minimising floor and ceiling artefacts and other sources of measurement error [169]. However, in *Study I*, cognition was assessed with the MMSE. While the MMSE has numerous advantages, it can suffer from both ceiling and floor effects. This means that having a higher score does not necessarily reflect lack of impairment, and a low score may not necessarily reflect definite impairment [272]. Moreover, the MMSE does not include items that assess processing speed and attention/executive functions. For these reasons, the MMSE may not be sensitive to subtle cognitive changes, especially in well-educated adults such as the SNAC-K participants. Nevertheless, the MMSE is sensitive to variation in macro-structural brain atrophy [273]; hence

a suitable measure in *Study I*. Dementia diagnoses in all studies were carried out by trained and qualified neurologists or neuropsychologists according to standard criteria and the DSM current at the time (DSM-III-R or DSM-IV).

5.7.2 Selection bias

A major point of consideration regarding our study designs is the study population and how it was selected. All participants from the respective datasets were invited to participate as older adults (including middle aged-adults in SATSA) who are then followed up, either with longitudinal or cross-sectional assessments, linkage to registries, or mortality data. In such populations, there is a healthy selection that is essential to consider when interpreting findings, especially related to cognitive or health outcomes in older adults. For example, oral health may be related to selective mortality, meaning that if people with poorer oral health have poorer health in general, and thus higher mortality in earlier ages, the surviving cohort will include participants with underestimated exposures and healthier individuals. Indeed, in all studies, those with missing oral health assessment or olfactory testing respectively, also had lower cognitive scores and overall poorer health. It is possible that if these participants had been included, the association would have been even stronger as our samples, MAP and SNAC-K in particular, had very high baseline cognitive function.

Selection bias may also occur due to missing data or attrition and can be a problem in the statistical models. Missing data points are managed in the mixed models, albeit, with the assumption that missing is at random, which as discussed cannot always be assumed. In addition, participants with only baseline assessments contributed to the intercept estimates and not to the slopes. It is possible that those that participated in less follow-up assessments are different regarding to the exposure, outcome or general health. The survival bias, was perhaps the most problematic when assessing the risk of dementia by Eichner categories in *Study II*. The stark difference in mortality among the Eichner categories may be the reason why compared to Eichner A, Eichner B and C seemed protective against dementia, as these participants were on average older and had more severe health burdens.

5.7.3 Confounding

A confounder is a known risk factor for the outcome that is associated with but not caused by the exposure [271]. In essence, a confounder makes the exposure more likely and in some way independently modifies the outcome, making it appear that there is an association between the exposure and the outcome when there is none, or masking a true association. Confounding is likely never completely accounted for, particularly unknown or unmeasured (residual) confounding. However, collecting adequate relevant information about the study participants, confounding could be addressed through adjustment, stratification, or matching.

In relation the oral health-cognitive decline association, we hypothesised based on previous work that factors such as age, overall health, functionality, depression, and SES could be confounding variables. For example, in a cross-sectional study using the SNAC-K population, tooth loss was found to be associated with a faster decline in functional status assed through walking speed [176]. Moreover, lower SES has been associated with lower levels of cognition, as well as a limitation for seeking dental care [60,65]. These factors were accounted for by adjusting for education, childhood SES, multimorbidity, and functional status (walking speed), which did not affect the observed associations in *Studies I* and *II*. Regarding cardio- and cerebrovascular diseases, inflammation and the *APOE* ε4 allele in *Study I*, these were not considered as confounders, rather factors which may explain the observed association based on previous literature [188]. In *Study II*, the exposure was very strongly related to age, therefore, we used age as time scale in all analyses, as the risk is expected to change more as a function of age rather than follow-up time. Moreover, especially in observational studies, it is difficult to establish if a proposed confounder is a consequence of the exposure, in which case, it should not qualify as a confounder.

Factors such as smoking status, diabetes, and hypertension have in previous studies been related to both olfactory ability and worse cognitive outcomes [252]; however, as these were not related to odour identification in the MAP study sample, we did not adjust for them in *Study III* in the favour of parsimony.

5.7.4 Generalisability and validity

There are different types of validity that should be considered. Internal validity is the extent to which an observed association supports a hypothesis of cause and effect, within the context of a particular study. External validity (generalisability) entails that the relationship identified in one study population should be transferable to another (general) population [274]. Lastly, the validity of measures used in the study depends on how well it measures what we actually intend it to measure.

In *Study I*, the study population consisted of highly educated and relatively healthy older adults. This is true in particular for the MRI subsample, which was healthier and more independent than the full study population. It is possible that this sample differs from the general population, which therefore compromises the generalisability of our results. Nevertheless, the SNAC-K population could be generalised to older European population with similar demographic backgrounds. Moreover, the findings were in support of with the greater part of previous work, upon which the hypotheses of this study were based on. In regards to the validity of the tooth loss variable in SNAC-K, previous studies have shown that self-report can give moderately reliable measures for tooth loss, whereas it does not perform well in reporting conditions periodontal disease or gingivitis. However, for a measure to

be valid, it needs to measure what we want it to measure, in this case, poor dental health, reflected in the extent of tooth loss. As we did not have information on the number of teeth, it could be that participants in the "no tooth loss" (own teeth only) group, did in fact have tooth loss to some extent, but not enough to consider themselves in the other categories. The potential consequence of this could be an underestimation of the true association.

The SATSA sample is more representative as it includes twins from the whole of Sweden. The participants included in SATSA grew up in a society with large class differences and widespread poverty. However its transferability to the cohorts growing older today in Sweden might be limited. This is particularly true for dental care, which has seen substantial improvements in recent years. Moreover, the proportion in the Eichner categories were identical to a recent study investigating the relationship between occlusal contacts and cognitive decline in a Japanese sample of 80 year-old adults. Although this sample was slightly older on average, it is interesting and reassuring that the proportion of the Eichner categories are comparable among two study populations, differing in lifestyle. Furthermore, the Eichner index is considered as a valid assessment of masticatory function [177]; nevertheless, other components of masticatory function such as bite strength, jaw mobility, or salivation were not included, which may have underestimated our findings.

The participants in MAP were volunteers who were not randomly selected from the community, were generally well educated and scored high on cognitive tests. Therefore, the MAP participants may not represent the diversity in race, SES, and health conditions of the general population in the United States. Moreover, in *Study III,* we limited our study sample to participants who had undergone MRI examination; this sample was healthier and had better olfactory performance than the full MAP population. This may have affected the magnitude of our results toward an underestimation. Despite this, the results of *Study III* were largely in support of the previous studies in the olfactory-cognition field, in addition to confirming previous work with the MAP study population. Related to this issue, the study sample in *Study IV* was restricted to those with at least one concurrent assessment of episodic memory and odour identification. The excluded participants were older, were in worse physical health and less educated, which likely would have implications for the trajectories we identified, especially as two of the classes had little to no decline in episodic memory during the eight years of follow up. Considering the age of the study sample, this may indicate possible selection bias, which may have implications for the generalisability of the findings. Moreover, the B-SIT has been found to be internally consistent, and its scores are in agreement with scores on the 40-item UPSIT, from which it was derived [115,169,275].

6 CONCLUSIONS

Based on the findings from the four constituent studies, the following conclusions can be drawn regarding the overall research question of this doctoral project.

Firstly, poor oral health is associated with cognitive decline, particularly fluid/spatial abilities and brain morphological differences, which could indicate a possible pathway of reduced blood flow to frontal brain areas, or neuronal injury through inflammatory pathways (**Figure 12, A**). In regards to the theoretical perspectives discussed in the introduction, these findings implicate oral health in both the inflammatory theory, as well as the sensory deprivation theory of ageing. This is important to consider in future studies, depending on the research aim.

Secondly, *Studies III* and *IV* confirm previous evidence regarding the close nature between olfaction and cognition. The findings suggest that olfactory impairment can predict decline in several cognitive domains, most markedly in episodic memory. This supports the claim that odour identification presents high diagnostic value for clinical outcomes associated with neuropathological changes, such as AD dementia (**Figure 12, B**). Moreover, episodic memory and odour identification follow similar trajectories in ageing, but decline in odour identification is not always accompanied by decline in episodic memory. In such individuals, the olfactory impairment may reflect peripheral damage or impairment, rather than representing pre-clinical dysfunction. Therefore, the aetiology of olfactory impairment is important to consider if olfactory tests should be utilised for screening or diagnostic purposes in people at risk for dementia.

In conclusion, the findings of this doctoral project demonstrate that poor oral health is associated with accelerated cognitive decline and brain ageing in old age, whereas, olfactory deficits predict cognitive decline and may reflect a loss of brain integrity in old age.

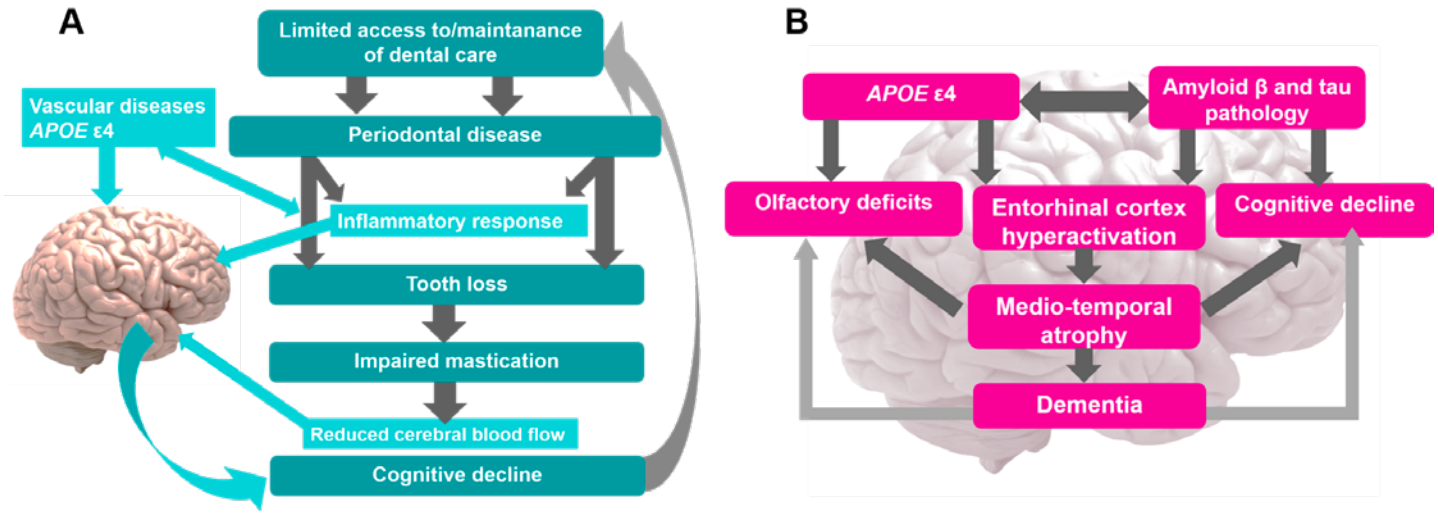

Figure 12. Proposed pathways linking oral health and olfactory function to cognitive impairment and brain integrity, based on the findings of this doctoral thesis in the context of previous literature. A) Limited access/maintenance of dental care may lead to severe oral health problems such as periodontal disease, resulting in tooth loss. Poor oral health increases inflammatory burden and reduces sensory input, thereby negatively impacting the brain and cognition in old age. B) The presence of one or more *APOE* ε4 allele and neuropathology could independently or synergistically impact olfactory and cognitive function. The medial-temporal cortex is vulnerable to neurodegeneration, which may lead to dementia, representing a shared pathway affecting olfactory and cognitive function.

7 FUTURE DIRECTIONS

Future research in oral health and olfactory function in relation to cognitive ageing has several possible avenues.

A few human and animal studies have shown beneficial effects of dental rehabilitation by increasing cerebral blood flow [276], and even reversal of cognitive impairment in mice [277]. Dental implant interventions are a promising avenue for future research; however, the costs involved are great, often requiring the participants themselves to cover the expenses of rehabilitation. This poses a great challenge, as participants will be difficult to recruit and will be extremely selected, limiting the generalisability of such studies. Nevertheless, orofacial medicine today in countries like Sweden is of very high quality, which in combination with increased awareness of the specific requirements of older adults and the need of equal access to dental health care, is very promising.

Secondly, more research is warranted regarding the mechanistic pathways linking oral health with cognitive decline, in order for it to be relevant in preventative measures. For example, the role of inflammation and vascular disorders has not been resolved as of yet. Future studies with clearer timelines between tooth loss, inflammatory responses, and cardiovascular diseases or events, are needed to elucidate this question.

Third, both oral health and olfactory function may influence the quality of dietary intake and nutritional status. However, more work is warranted regarding how and when poor oral health or olfactory function may be related to risk of malnutrition, in particular in a patient who is already undergoing cognitive changes, which may have implications for prognosis. This is important for geriatricians and other health care professionals to consider when planning the care of a patient.

Lastly, while olfactory decline and impairment is sensitive to underlying pathological processes, it may not necessarily reflect such pathology, and in some cases may even be independent of it. Therefore, further research is needed to take into account the aetiology of olfactory impairment, in order to establish its diagnostic utilisation in people at risk of cognitive impairment and dementia.

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10 APPENDIX

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991-2019

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hilleråas Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hilleråas Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.

Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Westerbotn Margareta. Drug use among the very old living in ordinary households- Aspects on well-being, cognitive and functional ability.

Rehnman Jenny. The role of gender in face recognition. (Stockholm University)

Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.

Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.

Livner Åsa. Prospective and retrospective memory in normal and pathological aging.

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.

Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

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Appendix Table 1. The assessments of cognitive functions and dementia used in this doctoral project.

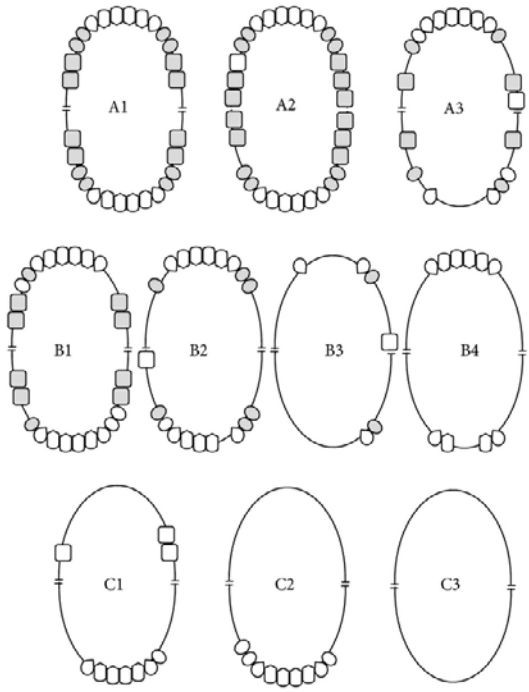
SNAC-K (n=3363)	SATSA (n=595)	MAP (n=1919)
Global cognitive function test		
MMSE	MMSE	MMSE
	Global cognition composite	Global cognition composite
Cognitive domains tests		
	Perceptual speed	**Perceptual speed**
	Symbol digit test	Symbol Digit Modalities Test
	Figure identification test	Number Comparison
		Modified Stroop-Neuropsychological Screening test
	Semantic memory	**Semantic memory**
	Names-faces recognition test	15-item form of the Boston Naming Test
	Synonyms	Verbal Fluency
		15-item version of the National Adult Reading Test
	Working memory	**Working memory**
	Digit span backwards	Digit Span Forward
		Digit Span Backward
		Digit Ordering
	Episodic memory	**Episodic memory**
	Thurstone's picture test	Word List Memory
		Word List Recall
		Word List Recognition
		Immediate and delayed recall of the East Boston Story and of Story A from Logical Memory of the Wechsler Memory Scale-Revised
	Spatial/fluid abilities	**Visuospatial ability**
	Figure logic, Block design	15 item form of Judgment of Line Orientation
	Card rotation tasks	16-item form of Standard Progressive Matrices
	Verbal abilities	
	Information & Analogies (WAIS sub-tests)	
Dementia diagnostic criteria		
DSM-IV, NINDS-ADRDA for AD‡ NINDS-AIREN for VaD‡	DSM-III-R & DSM-IV NINDS-ADRDA	

AD=Alzheimer's disease; VaD=Vascular dementia; MMSE = Mini Mental State Examination; WAIS=Wechsler Adult Intelligence Scale. NINDS-ADRDA= National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

Appendix Table 2. Comparison of the oral health measures and proportions in SNAC-K and SATSA study populations.

	Study population	
Oral health measure	**SNAC-K, n (%)**	**SATSA, n (%)**
Own teeth only	2105 (77.5)	179 (32.9)
Own teeth and partial or full denture	334 (12.3)	137 (25.1)
Complete tooth loss, with partial or full dentures	198 (7.3)	207 (16.5)
Complete tooth loss, no dentures	8 (0.3)	21 (9.2)
Implants	70 (2.6)	0 (0.0)
Median nr of teeth, IQR	-	20 (4-25)
Eichner Index	-	
A		147 (27.0)
B		169 (31.1)
C		228 (41.9)
Self-reported chewing problems		-
None	2345 (86.5)	
Mild	232 (8.6)	
Severe	134 (4.9)	
Self-reported periodontal disease	-	
Yes		417 (79.4)
No		108 (20.6)
Self-reported gingivitis	-	
Yes		105 (19.4)
No		437 (80.6)
Total	2715	544

Appendix Figure 1. Eichner Index categorisation.



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