Dietary patterns among older adults

With focus on dementia and related biomarkers

Jessica Samuelsson

Department of Psychiatry and Neurochemistry
Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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jessica.samuelsson@neuro.gu.se

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To my friends and family

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Jessica Samuelsson

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg
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ABSTRACT

Background and aim: Diet is a lifestyle factor that can influence healthy ageing and the risk of developing dementia. Studies investigating dietary patterns among older adults in relation to dementia, and dementia-related factors, can provide insights that will enable precision nutrition in dementia prevention strategies. The aim of this thesis was to investigate nutrient- and dietary intake among older adults, to explore associations between dietary patterns and dementia-related biomarkers, and to investigate potential gene-dietary pattern interactions in relation to incident dementia.

Method: Data were derived from the population-based Gothenburg H70 Birth Cohort Studies, including the Prospective Population Study of Women in Gothenburg, Sweden. There were five birth cohorts of 70-year-olds (n= 2 246) that participated in the dietary examinations between 1971 – 2016.

Results: Findings from ***paper I*** showed that the intake of healthy foods and alcohol increased among 70-year-olds between 1971 – 2016, and that the proportion of 70-year-olds at risk of an inadequate nutrient intake decreased over time. ***In paper II***, we found associations between higher adherence to a western dietary pattern and preclinical Alzheimer's disease (pathological alterations but no apparent symptoms). In ***paper III***, we found interactions between dietary patterns and *APOE ε4* (genetic risk factor for Alzheimer's disease) status in relation to incident dementia, where *APOE ε4* carriers with a high adherence to a western dietary pattern had an increased risk of dementia, whilst *APOE ε4* non-carriers with a high adherence to a healthy dietary pattern had a reduced risk of dementia. ***In paper IV***, we found associations between higher adherence to a low-fiber/high-alcohol dietary pattern and thinner cortical thickness (a marker of neurodegeneration), and associations between higher adherence to a Mediterranean-like dietary pattern and better white

matter microstructural integrity (an early marker of cerebrovascular alterations).

Conclusion: The findings from this thesis provide insights on dietary intake among older adults, and dietary patterns that may influence the risk of developing dementia.

Keywords: Alzheimer's disease, Amyloid β, *APOE* genotype, Dementia, Dietary patterns, Diffusion tensor imaging, Neuroimaging, Older adults, Polygenic risk score, Tau, Time trends

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SAMMANFATTNING PÅ SVENSKA

I takt med att den äldre befolkningen ökar så ökar även andelen med demens. En hälsosam kost kan bidra till ett hälsosamt åldrande och minska risken för demens. En högre följsamhet till medelhavskostliknande kostmönster anses minska risken för demens, men det är fortfarande oklart i vilken omfattning och sammansättning olika kostmönster kan påverka risken. Det är också oklart om genetiska förutsättningar kan modifiera potentiella samband mellan kostmönster och risken att drabbas av demens.

Syftet med den här avhandlingen var att undersöka kost- och näringsintag bland äldre, att undersöka potentiella gen-kostmönster interaktioner i relation till insjuknande i demens, samt att studera potentiella samband mellan följsamhet till olika kostmönster och biomarkörer relaterade till demens.

Avhandlingen baseras på data från de populationsbaserade H70 studierna i Göteborg, samt på data från Kvinnoundersökningen i Göteborg. Det var 2 246 70-åringar som deltog i kostundersökningarna mellan 1971 – 2016. ***Projekt I*** ger en överblick av tidstrender i kost- och näringsintag bland fem kohorter av 70-åringar födda mellan 1901 – 1944. Sammanfattningsvis såg vi att intaget av hälsosamma livsmedel ökade över tid bland 70-åringar, samt att det var en lägre andel i risk för ett inadekvat näringsintag över tid. En motsatt trend var intaget av alkohol, där medelintaget var högst bland de 70-åringar som undersöktes 2014 – 16. I ***projekt II*** fann vi samband mellan en högre följsamhet till ett västerländskt kostmönster och preklinisk Alzheimers sjukdom (patologiska Alzheimers-relaterade förändringar men utan kognitiva symtom). *I* ***projekt III*** fann vi interaktioner mellan kostmönster och *APOE ε4* (genetisk riskfaktor för Alzheimers sjukdom) status och insjuknande i demens, där *APOE ε4* bärare med en högre följsamhet till ett västerländskt kostmönster hade en ökad risk för demens, medan icke-*APOE ε4* bärare med en högre följsamhet till ett hälsosamt kostmönster hade en minskad risk för demens. I ***projekt IV*** kunde vi se samband mellan högre följsamhet till ett låg-fiber/hög-alkohol kostmönster och tunnare cortex (markör för neurodegenerativa förändringar) samt samband mellan en högre följsamhet till ett medelhavskostliknande kostmönster och bättre mikrostrukturell vitsubstans integritet (markör för tidiga cerebrovaskulära förändringar).

Sammanfattningsvis bidrar den här avhandlingen med ökad kunskap om kost- och näringsintag bland äldre, samt med kunskap om kostmönster kopplade till demens och demensrelaterade faktorer.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Samuelsson J, Rothenberg E, Lissner L, Eiben G, Zettergren A, Skoog I. **Time trends in nutrient intake and dietary patterns among five birth cohorts of 70-year-olds examined 1971–2016: results from the Gothenburg H70 birth cohort studies, Sweden.** Nutrition Journal, 2019; Nov 6;18(1):66.

II. Samuelsson J, Kern S, Zetterberg H, Blennow K, Rothenberg E, Wallengren O, Skoog I, Zettergren A. **A Western-style dietary pattern is associated with cerebrospinal fluid biomarker levels for preclinical Alzheimer's disease - A population-based cross-sectional study among 70-year-olds.** Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2021; May 18;7(1):e12183.

III. Samuelsson J, Najar J, Wallengren O, Kern S, Wetterberg H, Mellqvist Fässberg M, Zetterberg H, Blennow K, Lissner L, Rothenberg E, Skoog I, Zettergren A. **Interactions between dietary patterns and genetic factors in relation to incident dementia among 70-year-olds.** European Journal of Nutrition, 2021; Oct 10;61(2):871-884.

IV. Samuelsson J, Marseglia A, Lindberg O, Westman E, Pereira B J, Shams S, Kern S, Ahlner F, Rothenberg E, Skoog I, Zettergren A. **Associations between dietary patterns and markers of neurodegeneration and cerebrovascular pathology: a population-based study.** Manuscript

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ABBREVIATIONS

Aβ	Amyloid beta
Aβ40	40 amino acid Amyloid beta
Aβ42	42 amino acid Amyloid beta
AD	Alzheimer's disease
AD-PRS	Alzheimer's disease polygenic risk score
APOE ε2	*apolipoprotein E ε2* allele
APOE ε3	*apolipoprotein E ε3* allele
APOE ε4	*apolipoprotein E ε4* allele
APP	Amyloid precursor protein
BMI	Body mass index
BMR	Basal metabolic rate
CMB	Cerebral microbleeds
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CVD	Cardiovascular disease
DASH	Dietary approaches to stop hypertension
DHA	Docosahexaenoic acid
DII	Dietary inflammatory index
DSM	Diagnostic and Statistical manual of Mental Disorders

DTI	Diffusion tensor imaging
E %	Energy percent
ECG	Electrocardiogram
EI	Energy intake
EOAD	Early onset Alzheimer's disease
EPA	Eicosapentaenoic acid
FA	Fractional anisotropy
GWAS	Genome wide association study
H70	The Gothenburg H70 Birth Cohort Study
ICD	International Classification of Disease
LD	Linkage disequilibrium
LOAD	Late onset Alzheimer's disease
MCI	Mild cognitive impairment
MD	Membrane density
MeDi	Mediterranean diet
MIND	Mediterranean-DASH intervention for neurodegenerative delay
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NFA	National Food Agency
NNR	Nordic nutrition recommendations
NPR	National patient register

PAL	Physical activity level
PC	Principal component
PCA	Principal component analysis
PET	Positron emission tomography
PPSW	Prospective Population Study of Women
PRS	Polygenic risk score
PSEN 1	*Presenilin 1*
PSEN 2	*Presenilin 2*
P-tau	Phosphorylated tau
PVS	Perivascular spaces
SNP	Single Nucleotide Polymorphism
SVD	Small vessel disease
T-tau	Total tau
VaD	Vascular dementia
WMH	White matter hyperintensities

1 INTRODUCTION

1.1 DIET AND AGEING

The amount of people reaching higher ages is increasing globally (1). Europe and North America have the highest number of older adults world-wide, and by 2050 one in four is expected to be over the age of 65 years (1). Projections for Sweden alone show the same development (figure 1). Improvements in living standards and healthcare are some of the major contributors to decreased mortality and increased longevity (2-4). The increase in life expectancy is positive, but also challenging as the amount of people living with chronic diseases and disabilities will increase with growing older populations. Older adults in Sweden are usually categorized as being "older" when they are over the age of 65 years (based on the general retirement age). Those categorized as "younger" older adults are usually between 65 – 79 years, and those categorized as "older" older adults are usually 80 years or older. However, chronological age does not necessarily reflect biological age and cut-offs can differ between studies and countries.

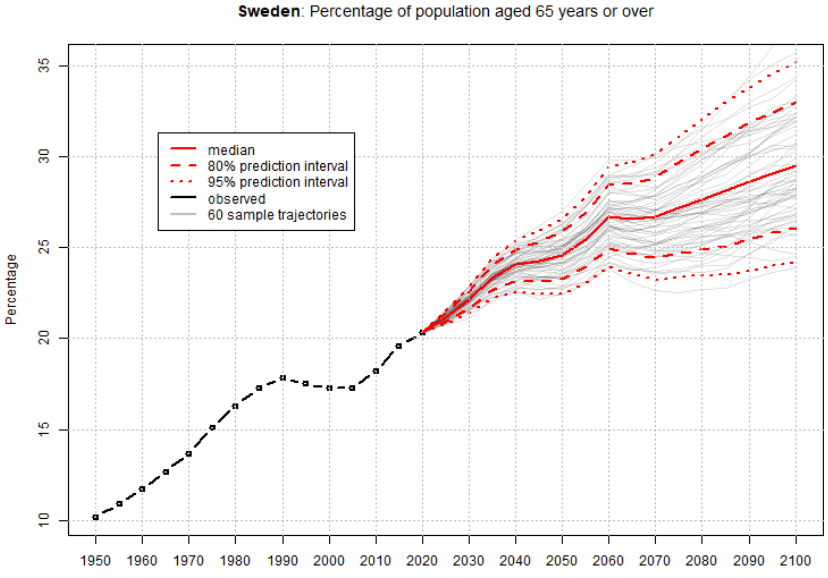

Figure 1. Projections of the increasing proportions of older adults over 65 years in Sweden. Source: United Nations, DESA, Population Division. Licensed under Creative Commons license CC BY 3.0 IGO. World population prospects 2019. http://population.un.org/wpp/

Ageing is a complex multifactorial process that is determined by genetic factors and influenced by environmental and behavioral factors (5, 6). There are individual differences in health perception, but the risk of disease and functional disabilities will increase with age (6). Multimorbidity (having ≥ two chronic diseases) is common among older adults and predicts functional decline and decreased quality of life (7). The number of healthy years lost due to disability has increased with longer lifespans, and the burden of disease is expected to increase with growing older populations (8). Disorders in older adults (≥ 60 years) contribute to about 50 % of the disease burden in high income regions, and to about 25 % of the disease burden globally (9). Non-communicable diseases such as cardiovascular diseases, malignant neoplasms (cancer), chronic respiratory diseases, diabetes, musculoskeletal diseases (e.g., sarcopenia and osteoporosis) and neurological and mental disorders (e.g., dementia) are leading contributory diseases (9). Non-communicable diseases are caused by genetic, physiological, environmental, and behavioral factors. Behavioral factors have the potential to be modifiable and several non-communicable diseases can be prevented or delayed with healthy lifestyle choices such as avoiding tobacco use, limiting alcohol intake, being physically active and having a healthy diet (9-12) (figure 2).

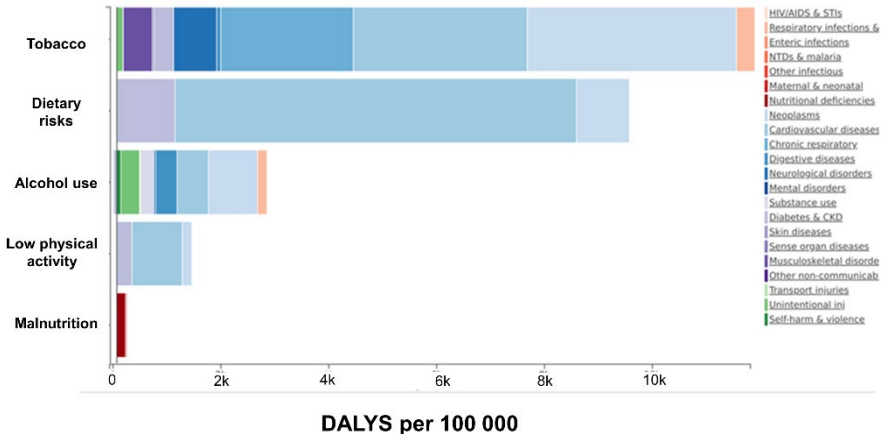

Figure 2. Disability-adjusted life years (DALYs) of tobacco use, dietary risks, alcohol use, low physical activity, and malnutrition in relation to diseases/conditions among older adults ≥70 years in Sweden, 2019. Source: Results from the 2019 Global Burden of Disease (GBD) Study (Licensed under CC BY 4.0, https://creativecommons.org/licenses/by-nc-nd/4.0/) (13), modified by author.

1.1.1 DIETARY RECOMMENDATIONS FOR OLDER ADULTS

Dietary guidelines for the general population in Sweden are provided by the Swedish National Food Agency (NFA) (14). The NFAs dietary guidelines are similar for older and younger adults, and aim to promote health and reduce the risk of non-communicable diseases such as diabetes type 2, cardiovascular diseases, and obesity. The guidelines recommend an increase in fruits, berries, vegetables and pulses (> 500 gram/day), nuts and seeds, fish and seafood (two-three portions per week), to choose wholegrain cereals before refined, change high-fat dairy products to low-fat, eat less red meat/processed red meat (< 500 gram/week), choose healthy vegetable fats (e.g., rapeseed oil, olive oil) before butter-based, and limit the intake of sugar and beverages/foods with added sugar, salt and alcohol (< 10 gram alcohol per day for women and < 20 gram alcohol per day for men) (figure 3). These guidelines are primarily based on the Nordic Nutrition Recommendations 2012 (NNR 2012) (14, 15). The NNR 2012 comprises the scientific basis for dietary reference values (e.g., vitamins and minerals) and food-based dietary guidelines in the Nordic and Baltic countries, and the sixth edition (NNR 2022) is planned for publication in 2023 (16). Food-based dietary guidelines based on the NNR 2012 recommendations are in line with several national dietary guidelines world-wide, including guidelines from the World Health Organization (17). The Swedish NFAs dietary guidelines are intended for generally healthy populations at all ages. However, individual adjustments of the dietary guidelines may be needed for older adults to reduce the risk of malnutrition if dietary intake, uptake, or metabolism are negatively affected by functional disabilities, disease, or anorexia of ageing (reduction in appetite and food intake caused by factors related to ageing processes) (18).

There are differences in the recommendations on protein and vitamin D intake between older and younger adults. A satisfactory protein intake is vital for the immune system and for maintaining muscle mass, function, and strength (19, 20). For older adults aged 65 and older, protein intake should contribute to 15 – 20 percent of the energy intake (E %), which equal about 1.2 gram protein per kg bodyweight and day (15). The higher protein recommendation is partially due to a declining anabolic response to protein intake among older adults. Vitamin D is a hormone that is synthesized in the skin at sun exposure. Food sources that naturally contain vitamin D are limited, but oily fish is a rich source. In Sweden, some foods (e.g., dairy products) have been fortified with vitamin D to increase the intake in the population. Older adults in Sweden are considered to have an increased risk of vitamin D deficiency due to factors such as less exposure to sun, lower availability of precursor in the skin, reduced

kidney function or an insufficient dietary intake (21). To reduce the risk of deficiency, older adults ≥ 75 years are recommended to supplement their diet with 20 µg (800 IU) vitamin D per day to obtain serum 25-hydroxyvitamin D concentrations of ≥ 50 nmol/L (15).

Figure 3. A quick overview of the dietary guidelines from the Swedish Food Agency. Source: Original by The Swedish Food Agency, with permission from the Swedish Food Agencies communication department, modified by author.

1.1.2 DIETARY INTAKE AMONG OLDER ADULTS

Dietary patterns within and between populations can vary depending on age, sex, culture, socio-economic and health-related factors. A systematic review showed that among community-dwelling older adults (≥ 65 years; majority of studies from Europe and North America) higher educational level, higher income, being married/living with others, having support from friends/neighbors, better social assets, female sex, younger ages (being between 65-75 years), and awareness of current dietary recommendations, have been associated with overall healthier dietary patterns, whilst loneliness and depression have been associated with less healthy dietary patterns (22). Diseases and functional disabilities among older adults may further affect dietary choices if the ability to buy, prepare, consume, or metabolize foods is altered (23).

In Sweden, three national dietary surveys have been performed among Swedish adults (age 18 – 80 years) by the NFA between 1989 – 2011 (24). Comparisons of results from these surveys showed that the intake of foods such as fruits, vegetables, wholegrain products, fish and shellfish, cream and alcoholic beverages increased between 1989 – 2011 in the Swedish adult population, whilst the intake of milk/yoghurt, buns, cookies, ice cream and soda decreased (24). Results from the 2010-11 survey also showed that older adults (65 – 80 years) generally had better dietary habits than younger adults (e.g., higher intakes of foods such as fruits, vegetables, whole grain products, fish and shellfish) (24). In the NFAs dietary surveys, the response rate decreased from about 70 % in 1989 to about 60 % in 1997-98 to less than 40 % in 2010-11 (24). The trend towards a decrease in participation rate during the past decades is in line with other epidemiological studies were decreasing response rates have become an increasing concern (25). With decreasing participation, there is an increasing risk of getting a sample that is not representative of the target population.

A previous study investigating dietary intake among four birth cohorts of 70-year-olds examined between 1971 – 2002 in the Gothenburg H70 Birth Cohort Study showed that nutrient density and intake of healthy foods were overall highest in the latest born birth cohort examined 2000-02 (26). Among the participants in the 2000-02 dietary examination, men with higher socio-economic status scored higher on a diet quality index score compared to those with lower socio-economic status (27). These differences were not observed among women (27). A Finnish study investigating nationwide dietary intake (data from cross-sectional health surveys from the National public health institute) among older adults (65 – 79 years) between 1985 – 2001 found

similar trends with an increase in healthier dietary patterns over time (especially among women) (28). However, there were disparities between occupational groups (e.g., former office employees had healthier dietary patterns than farmers) and married people had healthier dietary patterns than unmarried (28). A study on dietary intake and lifestyle factors among older adults (70 – 77 years) in the 1988 – 1994 US Framingham Heart study (MA, USA) and the Survey in Europe on Nutrition and the Elderly: A Concerted Action (SENECA) study (Belgium, Denmark, Italy, the Netherlands, Portugal, Spain, and Switzerland) found that dietary patterns differed between countries (29). They found that older adults in the Framingham study, and in the southern European countries, had overall healthier dietary patterns than older adults in the northern European countries (29). They also found that high quality diets were associated with less body fatness, non-smoking and higher physical activity level (29). In-between 1992 and 2000, dietary intake was investigated among older adults (≥ 60) in the EPIC-Elderly project, including ten European countries (Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the UK) (30). Two dietary patterns were found in these populations, one labelled "vegetable-based" (composed of e.g., vegetables, fruits, grains) and one "Sweet and fat-dominated" (composed of e.g., sweets, added fat, dairy products). They found that the vegetable-based pattern was associated with younger age, higher educational and physical activity level, higher body mass index (BMI), lower waist-hip ratio, and never or past smoking status, whereas the sweet and fat-dominated dietary pattern was associated with higher age, lower educational and physical activity level, lower BMI, lower waist-hip ratio, and never having smoked. There was a difference in adherence to the dietary patterns between the northern and southern European countries, with an overall higher adherence to the vegetable-based pattern in the southern European countries compared to the northern European countries (30).

1.2 DEMENTIA

Dementia is an increasing contributor to the global burden of disease (31). With increasing older populations, the global prevalence of dementia is expected to increase from approximately 50 million to 150 million by 2050, with about two-thirds living in low- and middle income countries (31, 32). In Europe, the prevalence is expected to have doubled by 2050. However, there are indications that the incidence of dementia could be decreasing in high-income countries (33-35). This decrease in incidence may be explained by improvements in cardiovascular treatments and health care, healthier lifestyle habits and higher educational level (34, 36).

Dementia is a syndrome characterized by cognitive impairments severe enough to decrease functional abilities and independence of everyday life. Dementia usually occurs after the age of 65 years, and comorbidities with other non-communicable diseases such as cardiovascular diseases (CVD) and diabetes are common (12, 37). Several diseases and injuries can cause dementia, and symptoms vary depending on stage and cause of dementia (38). Alzheimer's disease (AD) is the most common form of dementia (50 – 60 %), followed by vascular dementia (VaD, 10 –30 %) (39-42). Mixed pathologies are common (e.g., AD and VaD), especially among the oldest old (> 80 years) (39). The most common symptom is memory loss, but other cognitive, behavioral, and emotional symptoms can occur. Anxiety and impairments in learning, communication skills, executive functions, and complex attention, are some of many symptoms common in dementia.

1.2.1 ALZHEIMER'S DISEASE

AD is a progressive neurological disorder with a disease progression that starts several years before symptoms of the disease appear (41, 43). The accumulation of the protein amyloid beta (Aβ) into plaques surrounding brain neurons, and the protein tau into neurofibrillary tangles inside brain neurons are characteristics of AD pathology (40). Mechanistic pathways thought to be involved are Aβ aggregation, tau hyperphosphorylation, neurovascular dysfunction, cell-cycle abnormalities, inflammatory processes, oxidative stress, and mitochondrial dysfunction (40). The main hypothesis about the initiation of AD progression is the amyloid cascade hypothesis, which suggests an imbalance in production and clearance of Aβ that ultimately leads to neurodegeneration and dementia (44-46). Aβ plaques and oligomers (smaller accumulations of Aβ) and tau tangles are considered to interfere with synapse signaling in the brain, and disturb functions vital for neuron survival (47). How Aβ and tau interact is not clear (48). The amyloid cascade hypothesis suggests that the accumulation of Aβ leads to the accumulation of neurofibrillary tangles

in neurons (45, 46), whereas others have suggested that tau may accumulate independently and precede Aβ accumulation (49). The accumulation of plaques in the brain are believed to activate astrocytes and microglia cells from the immune system, causing an immune response that may be chronic due to constant activation of trying to clear tangles, plaques, and debris from dead and damaged neurons (41). Further, damage to blood vessels in the brain may contribute to cognitive impairments in AD by reducing nutrient delivery to neurons and reducing Aβ clearance from the brain (50). AD-related impairments in glucose metabolism in the brain may also decrease brain functions (41).

Clinical characteristics of AD are impairments in episodic memory (remembering previous events), aphasia (impaired ability to speak/understand spoken or written language), agnosia (the inability to recognise people, objects, sounds, shapes or smells), and apraxia (inability to correctly perform learned skilled movements), together with a variety of cognitive symptoms such as impaired decision-making, orientation, and judgement skills (40). The disease progression is often slow (approximately 15-25 years) with a gradual increase in symptom severity (43). The symptom continuum in AD has been described in five phases (41). The first pre-clinical phase can last from years to decades without the individual experiencing any symptoms of the disease (51). The second phase is called prodromal AD or mild cognitive impairment (MCI). At this stage the individual may experience very mild symptoms that does not interfere with everyday life (e.g., subtle problems with memory and language). Thereafter, the progression usually goes through three phases of mild (symptoms interfere with some everyday activities), moderate (symptoms interfere with many everyday activities) and severe (symptoms interfere with most everyday activities) AD (41).

AD can be categorized by age of onset as either late-onset AD (LOAD; clinical onset > 65 years) or early-onset AD (EOAD; clinical onset < 65 years). Sporadic LOAD is the most common form of AD, accounting for about 90 – 99 % of all AD (52, 53). The cause of sporadic LOAD is not known, but risk factors are considered multifactorial with complex interactions between genetic, environmental, and lifestyle factors (40). There is no cure for AD and pharmacological treatments are limited (41). This thesis will focus on factors related to the sporadic form of AD.

1.2.2 VASCULAR DEMENTIA

VaD is caused by injuries to brain tissue from not receiving blood, oxygen, or nutrients and/or by damages to vessels in the brain (39). Vascular pathology

can occur throughout the brain and contributes to vascular dementia through large vessel diseases such as large infarcts and hemorrhages and small vessel diseases such lacunes, cerebral microbleeds and white matter lesions (54). Cognitive impairments in VaD depends on what areas of the brain are affected.

Brain vascular pathologies can increase the risk of AD and coexist with AD, thereby worsening dementia symptoms (55). The prevalence of VaD varies depending on diagnostic criteria (42). Pure VaD may account for approximately 10 % of cases, often related to large infarcts (56). However, vascular brain pathology is common in AD and other dementias, and about 75 % of dementia cases showed signs of vascular pathology at autopsy (55, 56).

1.2.3 OTHER DEMENTIAS

This thesis will mainly refer to factors related to sporadic AD and VaD, but there are several other forms of dementia. Primary dementias such as AD are dementias caused by neurodegenerative disease. Lewy body dementia and Frontotemporal dementia are other types of primary dementias. Lewy body dementia (includes dementia with Lewy bodies and Parkinson's disease dementia) is the third most common form of dementia after AD and VaD among older adults over 65 years, followed by Frontotemporal dementia (57, 58). Frontotemporal dementia has an early onset, usually in mid-life (40 – 60 years), with symptoms such as language impairments, and behavioral and personality changes (59).

Dementia can also occur secondary as an effect of injuries or diseases (e.g., brain trauma, brain tumors, infections) with various symptoms (depending on cause and brain areas affected). Nutritional deficiencies such as B12 deficiency (primarily caused by a reduced uptake among older adults) and alcohol consumption are some of many secondary conditions that can cause dementia symptoms (60, 61). Secondary dementias can sometimes be reversable if the main cause can be treated in time.

1.3 DEMENTIA-RELATED BIOMARKERS

Cognitive, neurological, and neuropsychological testing (tests on cognitive, physical, and mental health) form the basis of the diagnostic procedures in AD and other dementias. However, biomarkers of AD and other dementias are increasingly incorporated to differentiate types of dementia and to detect signs of pathological changes before symptoms appear, thereby increasing the possibility for early interventions (62-64).

Biomarkers also play a crucial role in dementia research. In epidemiology, studies investigating associations between health-related factors and dementia-related biomarkers can provide information on factors that may prevent, delay, or affect disease progression. In intervention studies, biomarkers can be used as measurements for interventions and for disease progression. There are several forms of biomarkers that can detect and predict brain alterations related to dementia. Brain scans, such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) can identify causes of dementia (e.g., stroke and tumors) and alterations in structures and functions of the brain (62, 63). Cerebrospinal fluid (CSF) biomarkers can provide information on neurodegenerative processes related AD and other dementias (65). Also, blood-based biomarkers for AD are under development (66).

In this thesis, there will be a specific focus on CSF biomarkers for AD and brain MRI biomarkers related to overall and AD-specific neurodegeneration and cerebrovascular alterations.

1.3.1 CSF BIOMARKERS FOR ALZHEIMER'S DISEASE

The CSF (about 125 – 150 mL) circulates around the brain, spinal cord, and in the ventricles of the brain (67). The CSF has many vital functions such as providing buoyance and protection, provide nutrients, and remove waste products from the brain (68). Biomarkers from CSF can be used to diagnose and evaluate prognosis, progression, and treatment of neurodegenerative disorders such as AD (62). AD hallmark CSF biomarkers are Aβ42, phosphorylated tau (p-tau) and total tau (t-tau), and the combined analyses of Aβ42, t-tau and p-tau biomarkers are considered to provide the best accuracy when differencing AD from other dementias (figure 4) (62). The membrane bound amyloid precursor protein (APP) is enzymatically cleaved into different forms of Aβ, and the Aβ42 form (42 amino acids long) is the main component of Aβ accumulations in AD (69). CSF Aβ42 levels decreases in AD whereas

the Aβ40 form (40 amino acids long) remains unchanged. The ratio Aβ42/ Aβ40 has been suggested as a substitute marker for Aβ42 to correct for interindividual differences in Aβ production and clearance, and for handling of CSF samples that affects both Aβ forms (64, 70, 71). T-tau is a marker of neurodegeneration intensity in AD, and p-tau is a marker of neurofibrillary tangles within neurons (72). Decreased Aβ42 and increased concentrations of t-tau and p-tau have shown to highly predict AD, even before symptoms appear (51). Also, the ratio p-tau/Aβ42 has been suggested as a marker to discriminate AD from other dementias (e.g., VaD) (73). Amyloid pathology measured with PET can directly identify the accumulation of Aβ whereas Aβ42 biomarkers from CSF measures the soluble forms of Aβ. There is an inverse association between CSF Aβ42 concentrations and brain amyloidosis seen in PET imaging, indicating a physiological link between CSF concentrations and brain amyloidosis (62). However, pathological alterations may be detected at an earlier stage with CSF biomarkers compared with PET markers for Aβ42 and tau pathology (64). There can be differences in laboratories and techniques for measuring CSF, and cut-off levels for Aβ and tau pathology can vary between studies.

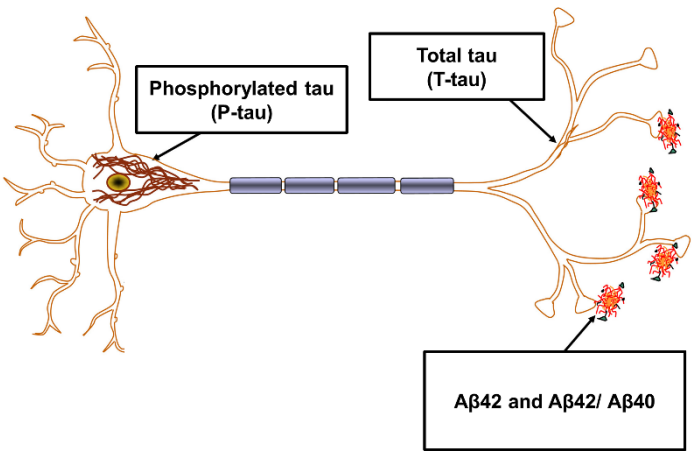

Figure 4. An illustration of a neuron and cerebrospinal fluid biomarkers related to pathological alterations in Alzheimer's disease. Source: Original by Blennow and Zetterberg 2018 (74), with permission from Wiley, modified by author.

1.3.2 DEMENTIA-RELATED MRI BIOMARKERS

Pre-clinical alterations, disease severity, and progression of AD and other dementias, can be detected with MRI. MRI is a sensitive, non-invasive, and safe method to measure processes related to neurodegeneration and cerebrovascular alterations (75, 76).

The cerebrum (largest part of the brain) is comprised of the outer cerebral cortex (gray matter) and underlying white matter. The cerebrum is divided into two hemispheres and has a large surface due to its folds (sulci) and ridges (gyri). The two hemispheres have four lobes (left and right sides): the frontal lobe (involved in e.g., personality and behavior), the temporal lobe (sides of the brain involved in e.g., memory and speech), the parietal lobe (middle part of the brain involved in e.g., identify objects, understand spatial relationships) and the occipital lobe (back part of the brain involved in vision). Subcortical regions include deep gray and white matter structures such as the corpus callosum, hippocampus, amygdala, and thalamus.

AD-related lesions caused by neurofibrillary tangles and amyloid plaques often appear first in the medial temporal lobe, including the hippocampus and entorhinal cortex regions (43, 48). As the disease progresses, brain lesions will increase and spread throughout brain regions (64). In the Desikan-Killiany cortical atlas, the cerebral hemispheres have been subdivided into 34 regions (77). Thinning of the cerebral cortex can be used as a marker of neurodegeneration, and AD signature cortical regions thought to be affected early in AD are the entorhinal, inferior temporal, middle temporal, and fusiform cortical regions (75, 78).

Commonly used markers for SVDs are white matter hyperintensities (WMH), cerebral microbleeds, enlarged perivascular spaces (PVS) and lacunes. These markers have independently, and combined into a global score, been associated with dementia (79).

White matter hyperintensities (WMH) have been associated with an increased risk of AD and VaD (80). WMH are brain white matter lesions of various sizes that are hyperintense on T-2 weighted MRI images, e.g., FLAIR images (81). WMH are considered a result of vascular pathologies such as small and large subcortical infarcts, but may also appear after e.g., deep intracranial hemorrhages (82, 83). Mechanisms involving WMH are not fully understood but hypoperfusion, neuroinflammation and thromboembolism may be involved (81). Early white matter microstructural alterations can be found with MRI diffusion tensor imaging (DTI) (84). DTI measures of white matter

integrity are considered to precede and predict WMH (85). Fractional anisotropy (FA) and mean diffusivity (MD) are commonly used DTI measures (85). FA measures the directional constraint of water diffusion, and MD measures the average rate of diffusion in any direction (85). FA is a summary measure of microstructural integrity that is highly sensitive to microstructural changes, but less specific regarding type of change (84). MD is an inverse measure of membrane density (84). Higher FA and lower MD values indicates better white matter microstructural integrity.

Lacunes are common among older adults, and have been associated with dementia (83). Lacunes are subcortical (e.g., basal ganglia, internal capsule, thalamus, pons, corona radiata, and centrum semiovale) round or ovoid fluid-filled cavities (about 3 mm to 15 mm in diameter) that usually originate from small subcortical infarcts (83).

Cerebral microbleeds (CMBs) are small (about 2 – 10 mm in diameter) brain hemorrhages. Deep CMBs have been associate with hypertension and other vascular risk factors, whereas lobar CMBs have been associated with cerebral amyloid angiopathy (83). CMBs are primarily located in the cortico-subcortical junction, cerebral hemispheres, brainstem, and cerebellum (83). The prevalence of CMBs in AD varies, but there seem to be an overall higher prevalence among those with AD compared to dementia-free older adults (86).

Perivascular spaces (PVSs) are fluid-filled round or ovoid shaped spaces (often smaller than 3 mm) that surround small blood vessels in the brain (87). The prevalence of enlarged PVSs on MRI increase with age, and PVS have been associated with SVD pathogenesis, AD, and other neurodegenerative and inflammatory disorders (87). Associations with vascular risk factors, inflammatory markers and neurological conditions can differ depending on what regions the PVSs are in the brain. PVSs in brain regions such as basal ganglia and the centrum semiovale have been associated with incident dementia (87). PVSs seem to be important for uptake of CSF to flush interstitial fluid and clear metabolic waste (87).

1.4 RISK FACTORS FOR DEMENTIA

Age is the strongest risk factor for dementia, but genetic, environmental and lifestyle factors can impact the risk across the life span (12). The Lancet commission report *Dementia prevention, intervention, and care: 2020* proposed twelve potentially modifiable risk factors accounting for around 40 % of the dementia cases globally: low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contacts, high alcohol consumption, traumatic brain injury and air pollution (12).

1.4.1 GENETIC RISK FACTORS

Mutations in the *amyloid precursor protein* (*APP*) gene, and the *presenilin1* (*PSEN1*) gene and *presenilin 2* (*PSEN2*) gene can cause autosomal dominant forms of EOAD. However, these forms of AD are rare, accounting for < 1 % of AD cases (88).

Several genetic variants have been associated with the risk of developing AD (89, 90). The *apolipoprotein E* (*APOE*) gene is the strongest genetic factor associated with the risk of developing sporadic AD (91). There are three common alleles of the *APOE* gene: the protective *APOE ε2* allele, the neutral *APOE ε3* allele, and the risk increasing *APOE ε4* allele (91). It has been suggested that the risk increase among heterozygous *APOE ε4* carriers could be tripled compared to not being a carrier, and that there could be a 15-time risk increase among homozygous carriers (40). The proportion *APOE ε4* carriers differ between countries, and the risk associated with AD seem to differ between populations, where Caucasian and Asian *APOE ε4* carriers seem to have a higher risk than African American and Hispanic *APOE ε4* carriers (92). Exactly how *APOE ε4* contributes to increased risk of AD is not known, but carriership seem to lower the age of onset (40). The *APOE* genotype affects Aβ and cholesterol metabolism, neuroinflammation and neurovascular function, which could further explain the association with AD (92). APOE is a cholesterol carrier that transports lipids to and from cell surface receptors, and the *APOE ε4* allele has been associated with hypercholesterolemia, hypertriglyceridemia, increased insulin resistance, atherosclerosis, and increased response to inflammation (93, 94). The *APOE ε4* allele may also impact the function of microglia and astrocytes, which are glial cells that contributes to important central nervous system (CNS) functions such as immune response, blood-brain barrier maintenance, synaptic support and preserving homeostasis (94, 95). Interactions between *APOE ε4* and lifestyle factors may play a mediating role in the risk of AD (95, 96).

However, not all AD cases are carriers of the *APOE ε4* allele, and other genetic variants may influence the risk of sporadic AD (89, 91). Through Genome-wide association studies (GWASs), 75 AD-related risk loci (genetic regions) have been found (97). These risk loci indicate that next to Aβ metabolism, cholesterol and lipid dysfunction, endocytosis, vascular factors, and the immune response play a role in the development of AD (43, 97). Non-*APOE* AD-risk modifying genetic variants are often combined into polygenic risk scores (PRSs) since they individually seem to have small modifying effect sizes (98). AD-related PRSs, both with and without *APOE ε4*, have been associated with age of onset and with the risk of developing AD (91, 99).

1.4.2 ENVIROMENTAL AND LIFESTYLE RISK FACTORS

Metabolic factors such as hypertension, hyperlipidemia, large waist circumference, and impaired fasting glucose, and related diseases such as obesity, ischemic disease, and diabetes have been associated with dementia (100). Obesity (BMI > 30) is an increasing concern among older adults, affecting between 18 – 30 % of older adults > 65 years worldwide (23). Obesity and hypertension in midlife have been associated with an increased risk of dementia (12, 101, 102). Excess body weight may increase the risk of dementia by contributing to brain lesions through vascular and metabolic pathways (103). However, reverse causality regarding excess weight and blood pressure have been seen in the years preceding dementia onset (most likely due to dementia-related processes) (101, 104-106).

A higher educational level may preserve cognitive function through a higher cognitive reserve (12). The cognitive reserve mechanism may involve increased connectivity in temporal and frontal brain areas (12). The theory behind cognitive reserve is that individuals with a high cognitive reserve may tolerate AD-related pathology better and thereby maintain cognitive function longer than those with a lower cognitive reserve (107). The risk reducing effect of a higher education may also be attained through intellectually demanding work and/or cognitively stimulating activities during leisure time (108, 109). Being socially active also seem to reduce the risk of dementia (110).

AD and other dementias are more common among women than men (111). These discrepancies may be caused by factors such as survival differences (women live longer), that men who survived over the age of 65 years may have a healthier cardiovascular risk profile (thereby lowering their risk of dementia), differences in biology (e.g., chromosomal or hormonal differences related to reproductive history), differences in distribution and experiences of social and

cultural factors, lower educational level among women (e.g., among women born in the early 20th century), and that genetic risk factors such as being an *APOE ε4* carrier may influence risk differently among women compared to men in regards to the development and susceptibility to AD pathology (41). However, findings concerning sex difference in the incidence of dementia among individuals of the same age have been mixed (41).

Physical activity in midlife and later life could reduce the risk of dementia, possibly through decreased risk of obesity, diabetes, and cardiovascular risk factors (12). A higher physical activity level may improve amyloid clearance and cognitive reserve, and has been associated with larger brain and hippocampal volume (108). However, less is known about the effect of specific types of exercise on dementia risk. Smoking is a risk factor for dementia that increases oxidative stress, and can affect vascular, inflammatory, and degenerative processes related to dementia (108). To quit smoking reduces the risk, even at older ages (112).

In observational studies, a low to moderate alcohol intake has been associated with reduced risk of dementia (61). The risk reducing effect has been linked to cardioprotective effects (e.g., increased HDL and a decreased risk of atherosclerosis through down-regulation of fibrinogen), and antioxidative effects of bioactive polyphenols in wine (especially red wine) (61). However, the cardioprotective effects have been questioned and alcohol is a toxin that can increase the risk of dementia through neurotoxicity, nutritional deficiency, neuroinflammation, changes in neurotransmitter systems and amyloid aggregation (108, 113). Results from studies investigating associations between a low to moderate alcohol intake and incident dementia have been inconclusive and there is no established level of alcohol that could be considered risk reducing (61). Further, methodological weaknesses have been found among studies investigating these associations, such as lack of standardization of alcohol use and level, inconsistencies in, or no control for, confounding variables, survival bias, and that former drinkers often were grouped with lifetime abstainers (former drinkers may have quit drinking due to health-related issues) (61). In the last Lancet commission report *Dementia prevention, intervention, and care: 2020*, a high alcohol intake was added as a risk factor for dementia (12).

Diet is a lifestyle factor that could influence the risk of dementia (114), either directly or indirectly by influencing the progression of other non-communicable diseases related to increased risk of dementia, such as obesity, diabetes, and cardiovascular diseases (12, 115, 116).

1.5 DIET AND DEMENTIA

Dietary factors may impact the risk of developing dementia at all ages across the lifespan (108, 117). Previous studies investigating associations between dietary factors and dementia are mainly observational but intervention studies examining the impact of diet and other lifestyle factors are increasing (108). Randomized controlled trials (RCTs) are considered gold standard to evaluate causality, and to measure the effectiveness of an intervention or treatment. However, dietary intervention studies can usually only be performed for shorter time periods, which limits the use of intervention studies in exploring causal associations between dietary intake and incident dementia. To combine findings from epidemiological studies with findings from interventions studies is therefore essential to increase our understanding of relations between dietary intake and incident dementia. Findings from exploratory cross-sectional studies and prospective cohort studies can provide insights on dietary patterns that may impact risk. These insights could be investigated further in interventions studies to enable precision nutrition in dementia prevention strategies.

Several foods, nutrients and bioactive components have been associated with the risk of developing dementia (118). A higher intake of dietary fiber, n-3 fatty acids (e.g., DHA, EPA), antioxidative vitamins (e.g., vitamins C, E), B-vitamins (e.g., vitamins B6, folate, B12), vitamin D, minerals (e.g., trace mineral selenium), and bioactive components such as polyphenols (e.g., flavonoids found in fruits and berries), have been associated with reduced risk of dementia (119). There has been a specific interest in the polyphenol resveratrol since resveratrol has been suggested as a risk reducing component in wine (119, 120). However, the bioavailability of polyphenols may be low, and resveratrol can also be found in more salubrious foods (e.g., grapes and lingonberries) that lacks the side effects of wine (119).

Foods such as fruits, vegetables, fish, nuts, and olive oil are considered to reduce the risk of dementia, whereas foods high in energy, saturated fatty acids and refined carbohydrates have been associated with an increased risk of dementia (114, 118, 121). However, foods and nutrients are not eaten in isolation but in combinations that forms dietary patterns. Recent years studies have therefore moved towards investigating the impact of dietary patterns on dementia risk rather than the effect of single foods, nutrients, and bioactive components.

1.5.1 DIETARY PATTERNS IN RELATION TO INCIDENT DEMENTIA

The impact of dietary patterns on dementia risk can differ depending on food combinations, as components in foods may synergistically interact and modify dementia risk (122). Healthy Mediterranean-like dietary patterns are considered to reduce the risk of dementia, whereas less healthy western-like dietary patterns are considered to increase the risk (114, 118, 123).

The Mediterranean diet (MeDi) is the most investigated dietary pattern in relation to cognitive decline and dementia (114, 123). The traditional MeDi is characterized by a high intake of vegetables, pulses, fruits, wholegrain products, nuts, olive oil, a moderately high intake of fish, a low to moderate intake of dairy products (primarily from cheese and yoghurt), poultry, and alcohol (primarily wine), and a low intake of red meat (124). However, other healthy dietary patterns, such as healthy/prudent dietary patterns, DASH (Dietary approaches to stop hypertension), MIND (Mediterranean-DASH intervention for neurodegenerative delay) and Nordic dietary patterns, have also been investigated in relation to cognitive decline and dementia (125-127). These dietary patterns resemble the MeDi in many aspects, but can differ in recommendations of amounts/servings of foods included, and in focus on specific foods/food groups, and/or consider cultural aspects of included foods. Healthy/prudent dietary patterns usually reflect national food-based dietary guidelines, such as the Swedish NFAs dietary guidelines based on the NNR 2012 (15). The main differences between the Swedish NFAs dietary guidelines and the MeDi are that the NFAs guidelines recommends limiting the intake of alcohol, to include dairy products but shift from full-fat to low-fat dairy products, and by recommending a wider range of vegetable oils than olive oil (15). The NFAs dietary guidelines also recommends lowering the intake of sweets, added sugar and salt. The Nordic diet is based on the NNR 2012 and MeDi, but focuses on Nordic locally produced food alternatives, such as root fruits (e.g., carrots, beetroot), cabbages, fruits/berries (e.g., blueberries, lingonberries, apples), wholegrain products (e.g., rye products), fish (e.g., salmon, cod, herring), pulses (e.g., peas and beans), rapeseed oil, and if meat is included in the diet, venison alternatives is recommended as the first choice (128). The DASH diet mainly differs from the MeDi by not including alcohol and by including recommendations on lower intakes of sweets, salt (sodium), total- and saturated fat (126). The MIND diet is a hybrid of the MeDi and DASH diets that emphasizes on foods previously linked to neuroprotection and dementia (e.g., green leafy vegetables and berries) (126). Results from previous studies investigating associations between healthy MeDi-like dietary patterns and incident dementia are inconclusive, showing either no

associations, or that a higher adherence reduces the risk of dementia (123, 126, 127, 129-135).

Western dietary patterns are characterized by foods high in salt and saturated fat such as red meat/processed meat and full-fat dairy products, products with added sugar, processed fast food/fried foods, and refined cereal products. Previous studies investigating associations between western-like dietary patterns and incident dementia are limited and findings are inconclusive, showing either no associations or that a higher adherence increases the risk of dementia (123, 136). However, people generally eat a mix of both healthy and less healthy foods, and it has been shown that higher adherence to a prudent dietary pattern may attenuate effects of a western diet on cognitive decline (122). Also, previous studies investigating associations between dietary patterns and incident dementia are heterogeneous (e.g., design, analyses, nutrient/food intake levels), which may explain some of the inconsistencies in results (121).

1.5.2 MECHANISTIC PATHWAYS LINKING DIET WITH DEMENTIA

Nutrients are transported into the brain via the blood-brain-barrier or the choroid plexus (the blood-CSF barrier) through several different transport systems (e.g., for glucose, folate, and vitamin C) to achieve nutrient homeostasis in the brain (137). Mechanistic pathways linking diet with dementia have not been established, but theories often involve inflammatory processes and lipid and glucose metabolism.

Theories on mechanistic pathways linking diet with dementia

Inflammatory processes have been linked to AD and related chronic diseases such as CVD, diabetes type 2 and obesity (138, 139). Weight gain and obesity can cause inflamed dysfunctional adipocytes that secret proinflammatory cytokines (locally and systematically) which causes a state of low-grade chronic inflammation that can lead to atherosclerosis and insulin resistance (140, 141). In recent years, several observational studies have examined relations between diet and chronic disease risk by using a dietary inflammatory index (DII) (142). In short, the DII is constructed based on food parameters that may either decrease or increase pro- and anti-inflammatory markers (143). The DII is based on 45 food parameters including nutrients (alcohol, dietary fiber, macro- and micronutrients), bioactive components (flavonoids), and food items such as garlic and ginger (143). MeDi and similar healthy dietary patterns are rich in components considered anti-inflammatory (e.g., n-3 fatty

acids, dietary fiber, vitamin C, flavonoids), and western-like dietary patterns are rich in components considered pro-inflammatory (e.g., saturated fat, trans fat) in the DII (142). In AD, chronic activation of microglial cells increases pro-inflammatory cytokines such as interleukin-1β, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (144). These inflammatory processes increase the risk of amyloidosis, neuronal death, and cortical thinning (144-146). The potential effect of diet on inflammatory processes may occur as a direct effect on AD-related neuroinflammatory processes and/or by inhibiting neuroinflammation via indirect immune pathways (e.g., gut microbiome and systematic circulation) (147). It has been suggested that healthy dietary patterns could reduce oxidative stress and neuroinflammation by inhibiting free radicals and cytokine production in activated microglial cells (immune cells in the brain) (147). On the other hand, western-like dietary patterns have been proposed to promote inflammatory processes in AD (148, 149).

In AD, disruptions in lipid and glucose metabolism have been suggested to affect production and clearance of β-amyloid and tau phosphorylation, and induce neurodegeneration (150). The lipid, glucose and energy metabolism are closely related, and disruptions in homeostasis of the metabolism have been associated with AD and dementia-related diseases (e.g., CVD and type 2 diabetes) (150). A healthy dietary pattern can help stabilize blood glucose levels among individuals with insulin resistance and diabetes, and reduce the risk of dyslipidemia, whereas unhealthy patterns may have adverse effects (151).

Dietary patterns and AD hallmark biomarkers

Most previous studies investigating associations between dietary patterns and AD hallmark biomarkers have investigated associations between MeDi-like dietary patterns and Aβ accumulation measured with PET (152). Some of these studies found that higher adherence to a MeDi-like pattern was associated with less Aβ burden among cognitively healthy individuals (153-158). One study that measured both Aβ and tau pathology among dementia-free individuals with subjective memory complaints or MCI found similar associations of less pathology among those with a higher adherence to a MeDi-like pattern (159). Two studies on a study population of women could not find any associations between MeDi-like dietary patterns and Aβ burden (160, 161). However, they found an association between a "junk food" dietary pattern and more Aβ burden (160). It has also been suggested that dietary patterns with a high glycemic load (a higher glycemic load is expected to give a greater raise in blood glucose levels after consumption) may be associated with increased Aβ pathology (152).

Dietary patterns and dementia-related brain MRI markers

Results from previous studies investigating associations between dietary patterns and dementia-related cerebrovascular and neurodegenerative MRI biomarkers are inconclusive, and few studies have investigated the impact of other dietary patterns than the MeDi (162, 163). Previous studies investigating associations between MeDi adherence and dementia-related MRI markers found either no associations or positive associations with grey matter volume (GMV), cortical thickness, cortical volume, hippocampal volume, white matter volume (WMV), and white matter microstructural integrity, and either no association or a negative association with WMH (162, 163). A study found a positive association between a healthy eating index and hippocampal volume (164). Another study found a positive association between hippocampal volume and a prudent dietary pattern, and a negative association between a western-like dietary pattern and hippocampal volume (165). A cross-sectional study investigating associations between both a western-like pattern (labelled processed) and a MeDi-like pattern and MRI markers of white matter microstructural integrity and brain volumes found no associations (166).

Gene-dietary pattern interactions in relation to incident dementia

It has been suggested that genetic predisposition could modify the impact of dietary patterns on dementia risk (95, 167). However, previous studies investigating interactions between dietary patterns and genetic risk in relation to incident dementia are rare (especially when it comes to other risk modifying genes than *APOE*). A previous study from the Rush Memory and Aging project found a borderline interaction between the MIND diet and *APOE ε4* in relation to AD among older adults, and that the risk reducing effect of the MIND diet was higher among *APOE ε4* non-carriers (126). The Three-City Cohort study found no interactions between a less healthy dietary pattern and *APOE ε4* status in relation to dementia (134). However, another Three-City Cohort study found an interaction between *APOE ε4* and a high glycemic load meal in relation to incident dementia, and that *APOE ε4* carriers who consumed afternoon snacks with a high glycemic load had a higher risk of dementia (168).

2 AIM

The overarching aim of this thesis was to study food- and nutrient intake among older adults, and to explore associations between dietary patterns and dementia and dementia-related biomarkers, by using data from the Gothenburg H70 Birth Cohort Studies.

Specific aims of paper I – IV

Paper I. The aim of paper I was to explore time trends in nutrient and dietary intake among five birth cohorts of 70-year-olds born between 1901 – 1944 in relation to the NNR 2012 dietary and nutrient recommendations.

Paper II. The aim of paper II was to explore cross-sectional associations between dietary patterns and AD hallmark CSF biomarkers Aβ (Aβ42 and Aβ42/ Aβ40), and tau (t-tau and p-tau), and the ratio p-tau/Aβ42 among dementia-free 70-year-olds born 1944.

Paper III. The aim of paper III was to investigate potential interactions between dietary patterns and genetic factors modulating risk for AD (i.e., *APOE ε4* status and non-*APOE* AD-PRSs) in relation to incident dementia among 70-year-olds born 1922 and 1930.

Paper IV. The aim of paper IV was to explore cross-sectional associations between dietary patterns and vascular and neurodegenerative MRI markers of relevance for dementia among dementia-free 70-year-olds born 1944.

3 MATERIALS AND METHODS

3.1 PARTICIPANTS

This thesis includes data from the population-based Gothenburg H70 Birth Cohort Studies (the H70 studies) (169). The H70 studies are multidisciplinary epidemiological studies examining older populations in Gothenburg, Sweden. Six birth cohorts of 70-year-olds have been followed longitudinally since the first study started in 1971. The participants were systematically selected based on birth year and birth dates via the Swedish Population Registry (169). All participants were 70 years old and registered residents in Gothenburg at their first examination. The studies also include participants from the Prospective Population Study of Women (PPSW) (170). The PPSW is a multidisciplinary study examining representative samples of women living in Gothenburg, Sweden. In the 1992-93 examination, women from the PPSW were included in the H70 study. In 2000-02, the two studies were merged. The overarching aim of the H70 studies is to study the impact of mental, somatic, and social health on functional ability and well-being in representative samples of older adults (169). The birth cohorts included in this thesis were the birth cohorts that included a dietary examination: 1901-02 (examined 1971-72), 1911-12 (examined 1981-83), 1922 (examined 1992-93), 1930 (examined 2000-02) and 1944 (examined 2014-16) (figure 5).

Birth cohort 1901-02

In 1971-72, all 70-year-olds living in Gothenburg and born 1901 and 1902 between July 1st, 1901, and June 30th, 1902, were systematically selected based on birthdates ending with 2, 5 or 8 (n=1148) (171). The 973 (response rate 85%) that participated in the examination were numbered from 1 to 5. Those with number 3 and 4 were selected for a dietary examination (n=389), and 370 (182 men, 188 women) participated (172).

Birth cohort 1911-12

In 1981-83, 1206 70-year-olds born 1911-12 were systematically selected based in birthdates ending with 5 or 6 (173). There were three samples, a medical control sample (n= 406), a register control sample (n=400), and an intervention sample (n=400). A total of 619 individuals from the medical control and intervention samples (n=806) participated in the basic examinations (response rate 77%). A subsample from the basic examination

was systematically selected for the dietary examination (n=303), and 262 (132 men, 130 women) participated (172).

Birth cohort 1922

In 1992-93, all 70-year-olds living in Gothenburg and born 1922 on days 6, 12, 18, 24, 30 of each month were invited to participate (n=753). There were 500 (response rate 66%) that participated. This study included women from the Population Study of Women in Gothenburg (PPSW) (174). A subsample of 250 individuals were selected for the dietary examination and 199 (63 men, 136 women) participated (172). All women were participants in the PPSW.

Birth cohort 1930

In 2000-02, all 70-year-olds living in Gothenburg and born 1930 on days 3, 6, 12, 18, 21, 24, 30 of each month were invited to participate (n=880, effective sample n=852). This study included women from the Population Study of Women in Gothenburg (PPSW) (175). A total of 604 (71%) participated. All participants were scheduled for the dietary examination and 554 (233 men, 321 women) participated, 255 of the women were participants in the PPSW (26).

Birth cohort 1944

In 2014-16, all 70-year-olds living in Gothenburg and born 1944 on dates ending with 0, 2, 5, or 8 were invited to participate (n=1839, effective sample n=1667) (169). A total of 1203 (72%) participated. All participants were invited to take part of the dietary examination and 861 (387 men, 474 women) participated (176).

Study population of paper I

Paper I included a total of 2 246 (56 % women) participants aged 70 years with dietary data from the birth cohorts born 1901-02, 1911-12, 1922, 1930 and 1944, as described for each birth cohort above.

Study population of paper II

Paper II included participants with dietary and CSF data from the baseline examination of the 1944 birth cohort. All the participants were invited to take part in a lumbar puncture (LP) for CSF sampling. There were 430 individuals that agreed to participate, but there were pharmacological contraindications for 108 persons, leaving 322 (166 men, 156 women) participants with CSF data

(169, 177). There were 273 participants with both dietary data and data on CSF biomarkers Aβ42, t-tau, p-tau. Four participants were excluded due to dementia, leaving a final sample of 269 participants (138 men and 131 women). The ratio Aβ42/Aβ40 were calculated for 266 (136 men and 130 women) out of the 269 participants due to missing data for three of the participants.

Study population of paper III

Paper III included participants from the 1922 (baseline examination 1992-93) and the 1930 (baseline examination 2000-02) birth cohorts with dietary and genotype data. Out of the 753 participants with dietary data, there were 616 participants with genotype data. In the 1922 birth cohort, none of the men had genotype data. One participant was excluded due to no dementia status, 11 were excluded for having dementia at baseline, and two were excluded because they died during the baseline examination year, leaving a final sample of 602 (218 men and 384 women).

Study population of paper IV

Paper IV included participants with dietary and MRI data from the baseline examination of the 1944 birth cohort. All participants were invited to take part in a brain MRI examination (169). There were 791 individuals that participated. After quality control of the MRI scans, 42 participants were excluded. Out of these, there were 616 participants with both dietary and MRI data. Five were excluded due to dementia and one was excluded for not having data on dementia status, leaving a final sample of 610 (282 men and 328 women) participants.

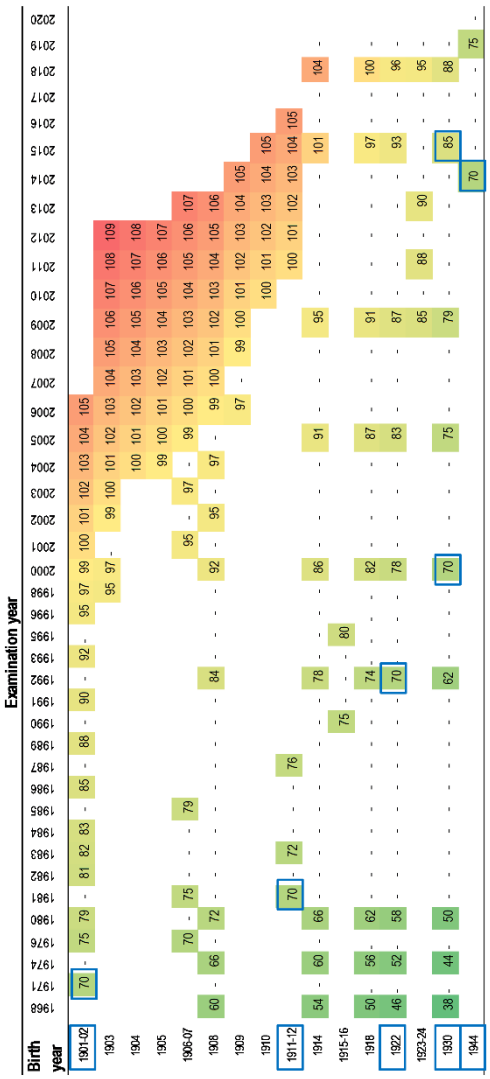

Figure 5. The Gothenburg H70 Birth Cohort Studies including birth years, examination years and age at examination. Birth cohorts that included a dietary examination are marked with blue brackets (birth year and age at examination). Source: Original picture created by Thomas Marlow, modified and published by Mellqvist Fässberg et al. 2019 (178), and further modified by author.

3.2 DATA COLLECTION

The H70-studies (including PPSW) include detailed personal examinations, assessing a wide range of health-related factors. The examinations have been practically identical at every examination to ensure comparability between birth cohorts and re-examinations (169). The participants were examined either at an out-patient clinic or at the home of the participant. Exclusion criteria were inability to speak Swedish, emigrated before study start, no contact or death. The examinations were performed by experienced research staff including nurses, psychologists, physiotherapists, dietitians, and medical doctors.

The examinations were divided into a general examination (performed during one full day or divided into two half-days) and additional examinations. The general examination is comprehensive and include physical examinations, psychometric testing (for cognitive health), and semi-structured interviews regarding somatic and psychiatric health, medical status, social and sociodemographic factors (e.g., education), activities of daily living and lifestyle factors (e.g., smoking, and physical activity). The physical examinations include anthropometric measurements (e.g., weight and length), blood pressure, and blood sampling (e.g., lipid and glucose levels), lung function and ECG (electrocardiogram). Participants were also asked to provide contact information to a proxy informant for close informant interviews. National hospital discharge diagnoses were obtained from the National Patient Register (NPR). Information on deaths were obtained from the Swedish population register. In the 2014-16 examination, all participants were invited to take part in additional examinations (after the general examination was performed) such as an MRI of the brain, CSF sampling, and a dietary examination.

3.2.1 DIETARY EXAMINATION

The diet history (DH) method was used at all dietary examinations. The DH method in the H70 studies include a semi-structured face-to-face interview, estimating dietary intake during the preceding three months. Results from the DH interviews in the 1944 birth cohort were registered as gram of food items usually consumed per day/week/month in a customized version of the computer program Dietist Net, containing the Swedish NFAs food and nutrient database of 2015. Pictures of food portions from the NFA were used during the interviews to estimate portion sizes of foods consumed. Results from the previous dietary examinations (1971 – 2002) were registered in the same way and calculated in the NFAs nutrient database (PC-kost) in 2000-02. Trained registered dietitians conducted the interviews at all dietary examinations, and the diet history method has been validated previously (179).

Dietary variables and construction of dietary patterns

Mean daily energy (kcal), macro- and micronutrients, alcohol, fiber, and food intake were calculated for all the birth cohorts based on results from the DH interviews. Reported food intake were manually categorized into food groups based on similarity of nutritional properties and biological classifications. In paper I, reported food intake were categorized into 35 food groups in accordance with the NFAs study on dietary patterns among Swedish adults (180). These food groups were modified with regards to aim, and statistical models used to derive dietary patterns in paper II – IV. For paper II and IV, that included the 1944 birth cohort, the food groups were modified into 22 food groups for paper II, and 27 food groups for paper IV. For paper III, that included the 1922 and the 1930 birth cohorts, the food groups were modified into 30 food groups (food group content can be found in the supplementary material for each paper). We chose data-driven models to explore dietary patterns in paper II – IV. For paper II and IV, dietary patterns (based on food groups) were derived with principal component analyses (PCA). For paper III, dietary patterns were derived with a reduced rank regression (RRR) analysis including the 30 food groups as predictor variables and estimated mean daily intake of vitamins E, C, and folate, dietary fiber, polyunsaturated fatty acids, saturated fatty acids, and alcohol. Factor loading thresholds of $\leq$ -0.20 and $\geq$ 0.20 were chosen for the PCA and RRR analyses when translating the factors from the analyses into dietary patterns. Factor loadings in between -0.2 and 0.2 (close to 0) can be considered weak and do not explain the variation in the response variables/dietary patterns well. We chose the threshold levels based on previous studies that have explored dietary patterns with PCA and RRR. To our knowledge there is no definite threshold, but several studies have chosen

(±) 0.2 as their threshold to define dietary patterns (181-184). Four dietary patterns were derived in paper II labelled "Western", "Mediterranean/prudent", "High-protein and alcohol" and "High total- and saturated fat" dietary pattern (figure 6). Two dietary patterns were derived in paper III labelled "Healthy" and "Western" (figure 7). Three dietary patterns were derived in paper IV labelled "Western", "Mediterranean", and "Low-fiber/high-alcohol" (not shown here since paper IV is not published). However, the dietary patterns in paper IV are similar to the "Western", "Mediterranean/prudent", and "High-protein and alcohol" patterns in paper II (figure 7).

The Goldberg method was used in paper I to evaluate potential misreporting of energy intake (185). Mean daily energy intakes (EI) were divided with calculated basal metabolic rates (BMR, calculated with equations for adults aged 60 – 74 years: 0.0386*body weight (kg) + 2.88 for women, and 0.0499*body weight (kg) + 2.93 for men) (185, 186). For individuals in energy balance, their EI/BMR should equal their physical activity level (PAL) (185). A cut-off limit for potential underreporting of energy intake were set at PAL 1.35 (a sedentary physical activity level) (185).

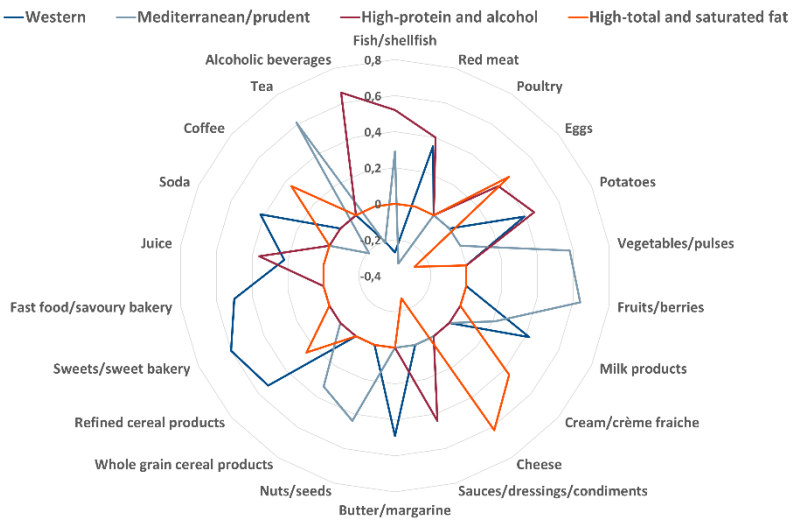

Figure 6. Dietary patterns derived with Principal component analysis in the 1944 birth cohort. Source: Original by the author, based on table 1 in the method section from Samuelsson et al. 2021 (187).

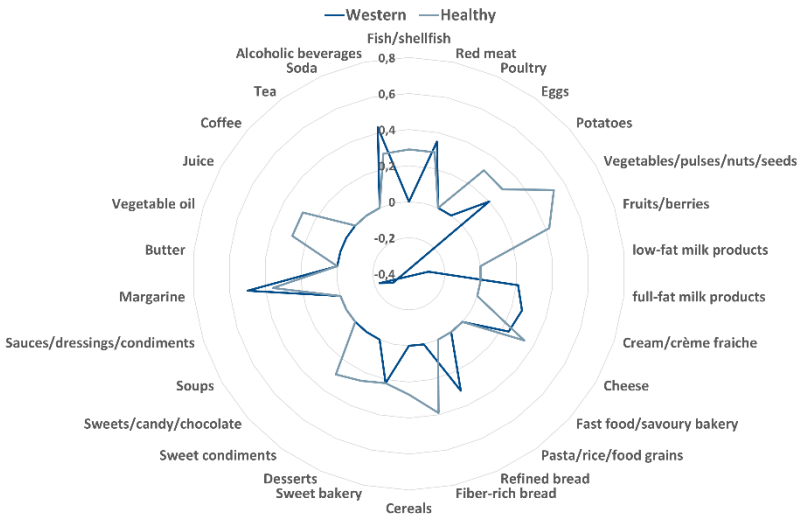

Figure 7. Dietary patterns derived with Reduced rank regression analysis in the 1922 and the 1930 birth cohort. Source: Original by the author, based on table 1 in the method section from Samuelsson et al. 2021 (188)

3.2.2 CSF SAMPLING AND CSF BIOMARKERS

CSF sampling was obtained via LP (169). CSF t-tau and p-tau (tau phosphorylated at threonine 181) were determined with a sandwich enzyme-linked immunosorbent assay (INNOTEST htau Ag abd PHOSPHO_TAU). Aβ42 was measured with a sandwich enzyme-linked immunosorbent assay (INNOTEST Aβ1-Aβ42). For the Aβ42/Aβ40 ratio, the V-PLEX Aβ Peptide Panel 1 (6E10) Kit (Meso Scale Discovery, Rockville, MD) was used.

CSF biomarkers Aβ42, t-tau, p-tau, and the ratios Aβ42/Aβ40 and p-tau/ Aβ42 were included in paper II as continuous variables. Aβ and tau were also categorized into binary outcomes. Aβ42, t-tau, p-tau were categorized into pathology (yes/no) as suggested by the A/T/N classification scheme (189). Cut-point values for pathology were ≤ 530 pg/mL for Aβ42, ≥ 80 pg/mL for p-tau, and ≥ 350 for t-tau (190-192). For the Aβ42/Aβ40 ratio, the cut-point ≤ 0.082 for pathology was determined by the bimodal cut-point of the data. Preclinical AD was determined by having both Aβ42 and t-tau and/or p-tau pathology (51).

3.2.3 NEUROPSYCHIATRIC EXAMINATIONS

The neuropsychiatric examinations were conducted either by a psychiatric nurse, a psychiatrist, or a medical doctor. The examinations include comprehensive psychiatric examinations, and an extensive battery of cognitive tests (169). The interviews include history of psychiatric conditions, suicidal behavior, sleeping patterns and dementia-related cognitive symptoms. Dementia-related symptoms were rated according to the Comprehensive Psychopathological Rating Scale (CPRS) (193), the Gottfries Bråne Steen-scale (194), and the Clinical Dementia Rating (CDR) (195). Cognitive function was rated in accordance with a Swedish version of the Mini-Mental state examination (196), and with assessments similar to the Alzheimer's Disease Assessment Scale (ADAS-COG) (197, 198).

Dementia diagnosis

Dementia was diagnosed following the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria using information from neuropsychiatric examinations and information from key informants (199). The procedures for the research diagnosis have been kept identical at all examinations to remain comparability between birth cohorts.

3.2.4 GENETIC ANALYSIS

DNA was extracted from samples of whole blood, according to standard procedures, in 2000-02. The DNA samples were genotyped at the University College London (UK), using the Neuro Consortium Array (neurochip) from Illumina. *APOE* genotyping was also performed at LGC Genomics in Hoddesdon (UK), using the KASP genotyping technology.

APOE genotype and AD-Polygenic risk scores

APOE genotype was divided into ε*4* carriers or ε*4* non-carriers (ε*4/* ε*2,* ε*4/* ε*3, or* ε*4/* ε*4)*. AD-PRSs were generated using stage 1 of a recent AD GWAS including clinically defined AD phenotypes (89). Single-nucleotide polymorphisms (SNPs) were selected using linkage disequilibrium (LD, refers to the linkage of genetic markers on a population level, and describes the degree of which an allele of a SNP is inherited with an allele of another SNP) clumping (extracting only one SNP per region). All variants in the *APOE* gene were removed to create non-*APOE* AD-PRSs. *P*-value thresholds ($p < 5e\text{-}8$, $p < 1e\text{-}5$, $p < 1e\text{-}3$, $p < 1e\text{-}1$) were used to create four AD-PRSs containing different amounts of SNPs, referred to as 5e-8 AD-PRS (including 15 SNPs), 1e-5 AD-PRS (including 57 SNPs), 1e-3 AD-PRS (including 1333 SNPs), and 1e-1 ADPRS (including 13 942 SNPs). The PRSs were calculated as the sum of the β-coefficient multiplied with the number/dosage of the effect alleles of each SNP (99). The AD-PRS scores were divided into three categories (i.e., tertiles) corresponding to low, middle, or high risk.

3.2.5 BRAIN MRI ACQUISITION

The participants were scanned on a 3.0T Philips Achieva system (Philips Medical Systems) using a 3D T1-weigthed Turbo Field Echo (TFE) for structural changes, a fluid attenuation inversion recovery (FLAIR) for detection of white matter pathology and T2 weighted images (169). White matter microstructural integrity was examined using DTI. Cortical reconstruction and volumetric segmentation of subcortical grey matter volumes were performed on the T1-weighted images using the FreeSurfer 5.3. Diffusion-weighted imaging (DWI) scans were analysed using the FMRIB Software Library's Diffusion Toolbox from FSL (FSL - FslWiki (ox.ac.uk)). Small vessel disease markers were defined according to the Standards for Reporting Vascular Changes on Neuroimaging and assessed by an experienced radiologist (83). WMH were automatically segmented with the Lesion Segmentation Tool 2.0.15 using parametric mapping software SPM12 (with quality control of the automatic segmentation).

Brain MRI markers

Brain MRI markers were generated to measure overall and AD-related neurodegeneration and cerebrovascular pathology in paper IV. Mean cortical thickness was used as a marker of overall neurodegeneration, and an AD cortical thickness signature derived by averaging cortical thickness of entorhinal, inferior temporal, middle temporal, and fusiform regions (from the Desikan Atlas) was used as a marker of AD-related neurodegeneration (77). A measure of mean hippocampal volume was derived by averaging the left and right hippocampal volume (adjusted for total intracranial volume). A global small vessel disease (SVD) score (range 0 – 3, indicating low to high burden) was constructed including measures of WMH volume (adjusted for total intracranial volume), CMBs, PVS and lacunes (79). Mean DTI FA and MD for the whole white matter skeleton were used as overall measures of white matter microstructural integrity.

3.2.6 POTENTIAL CONFOUNDERS

Information on potential confounders were obtained through semi-structured interviews and health examinations at baseline examinations (when the dietary interviews were performed). Sex, energy intake, BMI, physical activity level, and educational level were included as potential confounders in paper II, III, IV. Estimated mean daily energy intakes (kcal/day) were derived from the dietary examinations, BMI was calculated based on weight and height (kg/m^2), physical activity level was divided into three (paper III) or four categories (paper II and IV) based on a modified Saltin-Grimby physical activity scale (200, 201). Educational level was divided into two categories in paper II and III (cut-off threshold was compulsory primary education), and into three categories in paper IV (based on Swedish education classifications; compulsory primary education, secondary education, and higher education) (202). Smoking was included and defined as either smoking or not smoking in paper III, IV. In paper III, birth year, hypertension, diabetes, total cholesterol levels, and five principal components (PCs) to correct for population stratification (e.g., systematic differences in allele frequencies between ethnical groups within a study population) were included as potential confounders. There were no confounders included in the descriptive paper I.

3.3 STATISTICAL ANALYSES

Comparisons of characteristics in paper I were performed with linear regression models for continuous variables (characteristics as dependent variable and birth cohorts as independent variable) and chi-square test for categorical variables. Comparisons of characteristics in paper II – IV were performed with student´s t-test (mean values), Mann-Whitney U test (ordinal/not normally distributed continuous variables) and chi-square test (categorical values).

The main analyses for paper I – IV will be described for each paper separately.

Paper I

Linear regression analyses were used to explore time trends between 1971 – 2016, with mean EI/BMR, and mean intake of energy, macro- and micronutrients, alcohol, dietary fiber, and food groups as dependent variables, and the five birth cohorts examined between 1971 – 2016 as independent variable (the birth cohorts were categorized 1-5). In addition, student´s t-tests were used to compare means of the same variables between birth cohorts (two at a time). Chi-square tests were performed to explore potential differences between birth cohorts in the distribution of participants with an energy percent (E%) from macronutrients (the % energy each macronutrient contributes with to the total energy intake) in line with NNR 2012 recommendations, a micronutrient intake above average requirement intake (AR, according to NNR 2012), and consumption of foods. Pearson correlation coefficient analyses were performed between EI/BMR and BMI for each birth cohort separately. All analyses were stratified by sex.

Paper II

Linear and logistic regression analyses were used to explore associations between the dietary patterns and the CSF biomarkers, with the dietary patterns (component scores from the PCA, continuous variables) as independent variables and the CSF biomarkers as dependent variables (continuous and binary outcomes). The analyses were performed in two models, one unadjusted for confounders and one adjusted for sex, energy intake, educational level, physical activity level and BMI. Subgroup analyses of the linear regression models were performed stratified by sex and by sex and *APOE ε4* status (carrier/non-carrier).

Paper III

Cox regression analyses were performed to explore associations between the dietary patterns and the interaction variables (interaction variables of the dietary patterns and the AD-PRSs, and of the dietary patterns and *APOE ε4* status) as independent variables and incident dementia as outcome variable. The time variable in all the Cox regression models was calculated as time in years from baseline examination to either age at dementia diagnosis, age at death, or time to end of study. All Cox regression analyses were performed in two models, one adjusted for sex and birth year, and one adjusted for sex, birth year, energy intake, BMI, total cholesterol, diabetes, hypertension, education, smoking, physical activity level and five principal components to correct for population stratification. The interaction *p*-value threshold was set at < 0.1.

Paper IV

Linear regression analyses were used to explore associations between the dietary patterns as independent variables, and the MRI markers DTI FA, DTI MD, hippocampal volume, AD-signature cortical thickness, and total mean cortical thickness as dependent variables. Ordinal regression analyses were performed to explore associations between the dietary patterns as independent variables and the SVD score (four categories ranged between 0-3, indicating low to high burden) as dependent variable. The analyses were performed in two models, one adjusted for sex and one adjusted for sex, energy intake, BMI, educational level, smoking, and physical activity level. In addition, whole-brain surface-based analyses were performed in FreeSurfer 5.3 to explore unbiased associations between the dietary patterns and cortical thickness for the left and right hemisphere, adjusted for sex.

3.4 ETHICAL CONSIDERATIONS

All studies from 1976 to 2000-02 were ethically approved by the Ethics committee for medical research in Gothenburg. The 2014-16 examination were approved by the Regional Ethical review board in Gothenburg. All participants gave informed consent to participate according to the Helsinki declaration. If the participant was not able to give consent (e.g., due to dementia), consent was obtained from a relation with authority to approve. Information regarding potential risks, storage, and handling of personal data, expected duration of examinations, and the possibility to withdraw participation at any time was given before examinations. Results from examinations with potential medical implications were inspected by a medical doctor. If pathologies or an unknown disease were detected, participants were referred to an appropriate clinic for further examination and treatment. The examination load in the H70 studies can be considered demanding. However, the participants could choose to what extent they wanted to participate. Benefits of the study in relation to participant contribution have been considered. The participants receive a comprehensive health examination, which may be an incitement for participation and a potential explanation for the overall high participation rates.

4 RESULTS

Summarized results for each paper are presented in this chapter. A more detailed description of the results can be found in the articles and the manuscript in this thesis.

4.1 PAPER I

Samuelsson J, Rothenberg E, Lissner L, Eiben G, Zettergren A, Skoog I. **Time trends in nutrient intake and dietary patterns among five birth cohorts of 70-year-olds examined 1971–2016: results from the Gothenburg H70 birth cohort studies, Sweden**. Nutrition Journal, 2019; Nov 6;18(1):66 (176).

Comparisons of characteristics between the birth cohorts showed a decrease in the proportion of participants with a sedentary lifestyle (from 20 % to 3 % among women, and 12 % to 3 % among men), a decrease in the proportion of participants with ≤ compulsory education (from 84 % to 11 % among women, and 81 % to 15 % among men), and a decrease in the proportion of participants that smoked (from 12 % to 9 % among women, and 46 % to 7 % among men) between 1971 – 2016 (176). The participants were mainly community-dwelling (0 % to 4 % of the participants were institutionalized in the birth cohorts examined between 1971 – 2016). The proportion of married women increased among women (from 47 % to 69 %) but remained similar among men (between 79 % – 81 %) between 1971 – 2016. Mean BMI were between 26 – 27 at all examinations among both men and women (176).

Mean EI/BMR were above 1.35 (i.e., the cut-off value for potential underreporting of energy intake) among both men and women at all examinations between 1971 – 2016 (mean EI/BMR were between 1.40 (SD, 0.34) – 1.59 (sd, 0.43)) (176). Negative correlations between BMI and EI/BMR indicated that participants with a higher BMI tended to underreport their energy intake. This was found among both sexes and in all birth cohorts.

The results showed trends toward an increase in dietary patterns with a higher nutrient density, and a higher intake of healthy foods such as fish/shellfish, vegetables/pulses, fruits/berries, nuts/seeds among participants in the later born birth cohorts (figure 8-9, 12) (176). There was a shift in trend regarding dairy products in the 2014-16 examination, with a decreased intake in milk products (especially low-fat milk products), and an increase in cheese, cream, and crème fraiche (figure 10) (176). There was a decreased intake of less healthful foods such as sweet bakery, and sweet condiments while there was a

slight increase in candy/chocolate intake over time (figure 11) (176). Fiber intake increased between birth cohorts and was highest in the 2014-16 examination (mean intake 25 gram/day (SD, 8 g) for women and 27 gram/day (SD, 9 g) for men) (176). There were more participants with a micronutrient intake above average requirement (AR) levels (levels below AR are considered inadequate), and with a protein intake in line with protein recommendations for older adults ≥ 65 years in the later born birth cohorts (figure 12 and 13) (176). Alcohol intake increased over time, and about 1/3 of the participants had an alcohol intake above the upper limit recommended in the NNR 2012 (> 10 gram/day for women and > 20 gram/day for men) in the 2014-16 examination (figure 14) (176).

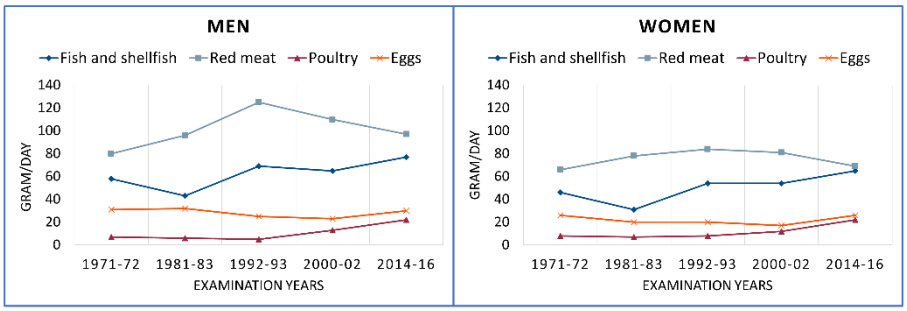

Figure 8. Mean gram intake per day of fish/shellfish, red meat/processed red meat, poultry, and eggs among five birth cohorts of 70-year-olds examined between 1971 –2016. Source: Original by the author, based on results published in Samuelsson et al. 2019 (176).

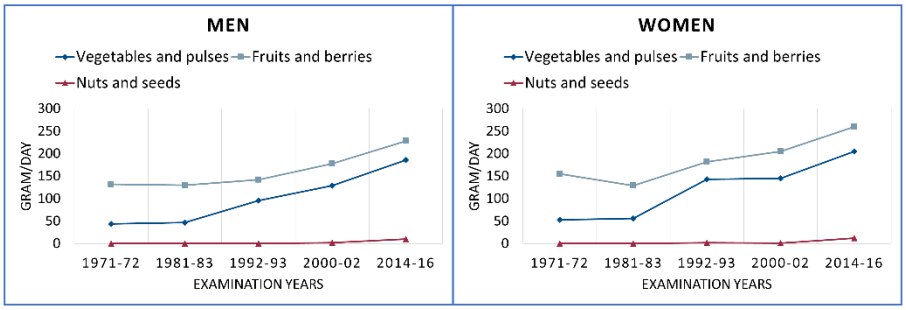

Figure 9. Mean gram intake per day of vegetables/pulses, fruits/berries, and nuts/seeds among five birth cohorts of 70-year-olds examined between 1971 – 2016. Source: Original by the author, based on results published in Samuelsson et al. 2019 (176).

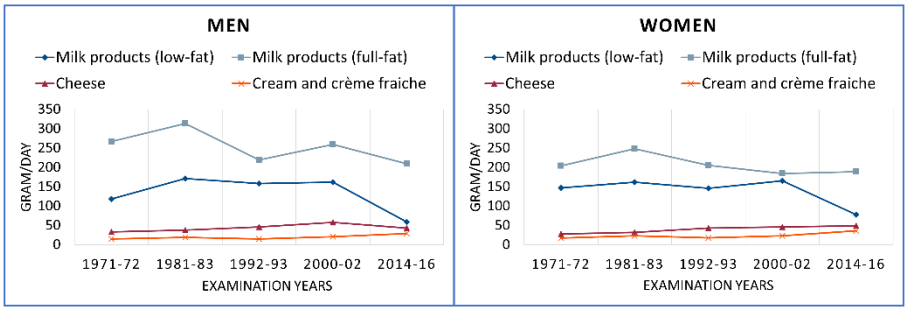

Figure 10. Mean gram intake per day of dairy products among five birth cohorts of 70-year-olds examined between 1971 –2016. Source: Original by the author, based on results published in Samuelsson et al. 2019 (176).

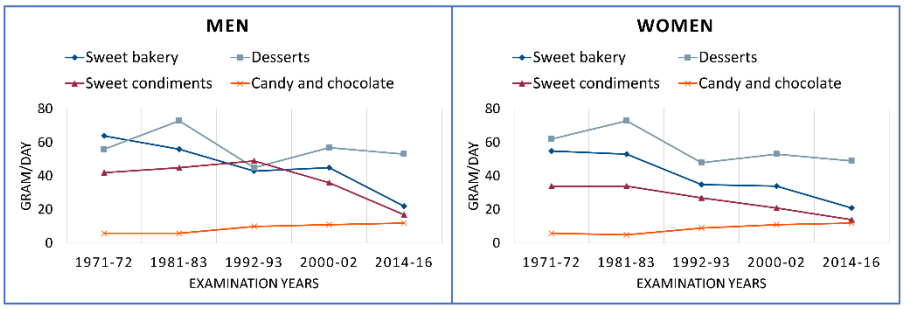

Figure 11. Mean gram intake per day of sweets among five birth cohorts of 70-year-olds examined between 1971 –2016. Original by the author, based on results published in Samuelsson et al. 2019 (176).

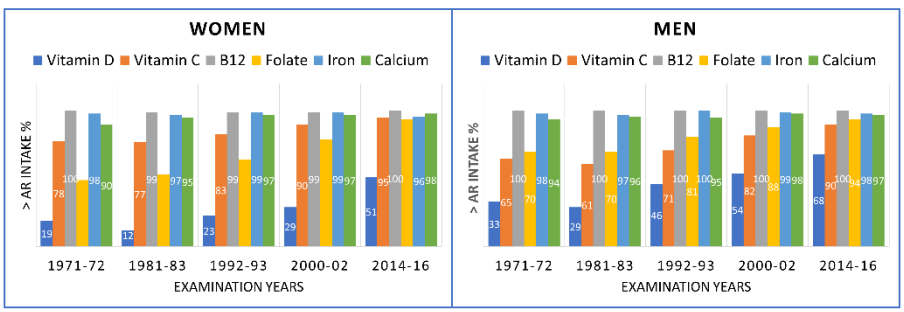

Figure 12. The proportion of 70-year-olds with a micronutrient intake above NNR 2012 average requirement (AR) levels. Source: Original by the author, based on results published in Samuelsson et al. 2019 (176).

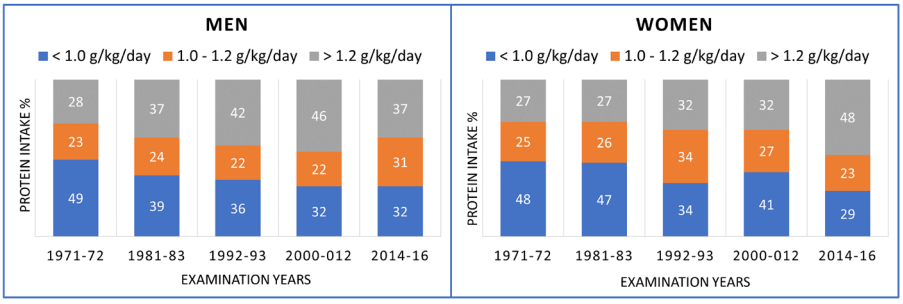

Figure 13. The proportion of 70-year-olds with a protein intake below (< 1.0 gram/kg bodyweight/day), according to (1.0 – 1.2 gram/kg bodyweight/day), or above (> 1.2 gram/kg bodyweight/day) NNR 2012 recommendations for generally healthy older adults ≥ 65 years. Source: Original by the author, based on results published in Samuelsson et al. 2019 (176).

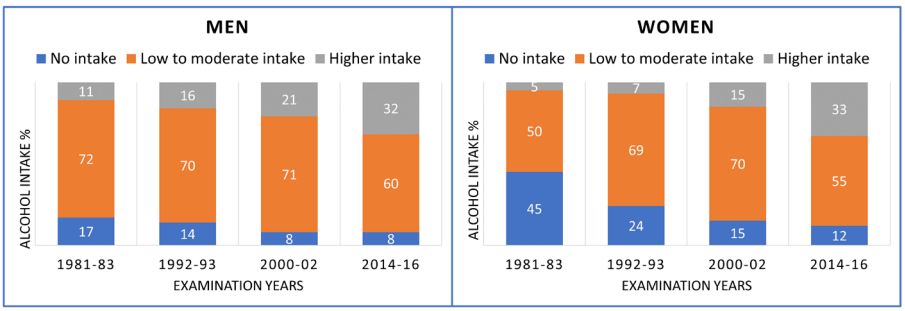

Figure 14. The proportion of 70-year-olds that reported either no intake of alcohol, a low to moderate intake (upper limit 10 gram/day for women and 20 gram/day for men based on NNR 2012 upper recommended limits/day), and a higher intake (above NNR 2012 upper recommended limits/day). The 1901-02 birth cohort was not included in the analyses containing alcohol since there was no gram data on wine and spirit consumption (only beer) in the 1971-72 dietary examination. Source: Original by the author, based on results published in Samuelsson et al. 2019 (176).

4.2 PAPER II

Samuelsson J, Kern S, Zetterberg H, Blennow K, Rothenberg E, Wallengren O, Skoog I, Zettergren A. **A Western-style dietary pattern is associated with cerebrospinal fluid biomarker levels for preclinical Alzheimer's disease - A population-based cross-sectional study among 70-year-olds.** Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2021; May 18;7(1):e12183 (187).

To explore representativeness of the CSF sample with dietary data, we compared characteristics and adherence to the dietary patterns between the dementia-free participants with CSF and dietary data and those with only dietary data (stratified by sex). There were no differences in dietary pattern adherence or characteristics (energy intake, BMI, MMSE score, physical activity level, education and *APOE ε4* status) between participants with and without CSF data, except for *APOE ε4* status among men (43 % were *APOE ε4* carriers in the CSF and dietary sample compared 31 % in the sample with only dietary data $p = 0.02$) (187).

The main findings in this study were that higher adherence to a western dietary pattern was associated with t-tau pathology (OR: 1.43; 95 % CI: 1.02 – 2.01 and pre-clinical AD (i.e., Aβ42 and t-tau and/or p-tau pathology) (OR: 1.79; 95 % CI: 1.03 – 3.10) (187). There was an inverse association between higher adherence to the high-protein and alcohol pattern and t-tau pathology (OR: 0.71; CI: 0.51 – 0.98) (187). However, this association was not found in the unadjusted model. We found no other associations between the dietary patterns and the CSF biomarkers in the binary logistic regression models.

No associations were found between the dietary patterns and the CSF markers in the linear regression models including the total sample (187). In subgroup analyses, positive associations were found between adherence to the western dietary pattern and t-tau and p-tau levels among women that were *APOE ε4* non-carriers (t-tau; B: 0.15; 95 % CI: 0.05 – 0.24) (p-tau; 0.12; 95 % CI: 0.03 – 0.21) (187).

4.3 PAPER III

Samuelsson J, Najar J, Wallengren O, Kern S, Wetterberg H, Mellqvist Fässberg M, Zetterberg H, Blennow K, Lissner L, Rothenberg E, Skoog I, Zettergren A. **Interactions between dietary patterns and genetic factors in relation to incident dementia among 70-year-olds.** European Journal of Nutrition, 2021; Oct 10;61(2):871-884 (188).

There were 125 participants that developed dementia during the study period. The mean follow-up time was 12.8 years (SD, 4.5 years, 7685.5 person-years), and the mean age of dementia onset was 80.2 years (SD, 4.9). There were no differences in age, sex, genetic risk, western dietary pattern adherence, energy intake, total cholesterol levels, hypertension, diabetes, physical activity level, educational level, and smoking between those that developed dementia during the study period and those that did not develop dementia. Those that did not develop dementia had a higher BMI (26 vs. 27), and a higher adherence to the healthy dietary pattern compared to those that developed dementia. There were more *APOE ε4* carriers among those that developed dementia compared to those that did not develop dementia (27 % vs. 40 %) (188).

Gene-dietary pattern interactions in relation to incident dementia were found for *APOE ε4* but not for the four AD-PRSs. *APOE ε4* non-carriers with a higher adherence to a healthy dietary pattern had a reduced risk of dementia, whilst *APOE ε4* carriers had not. On the other hand, *APOE ε4* carriers with a higher adherence to a western dietary pattern had an increased risk of dementia that was not seen among *APOE ε4* non-carriers (table 1) (188). In the total sample, no associations were detected between the dietary patterns and incident dementia (188).

Table 1. Associations between adherence to the dietary patterns and incident dementia among *APOE ε4* carriers and *APOE ε4* non-carriers

	Model 1[a]		*p* value	Model 2[a]		*p* value
	Dementia	n=125/602[b]		Dementia	n=121/573[b]	
Dietary patterns	**HR**	**CI**		**HR**	**CI**	
Healthy						
APOE ε4 non-carriers	0.79	0.65; 0.95	0.01	0.77	0.61; 0.98	0.03
APOE ε4 carriers	1.02	0.80; 1.30	0.89	0.86	0.63; 1.18	0.35
Western						
APOE ε4 non-carriers	0.98	0.81; 1.18	0.81	0.99	0.81; 1.21	0.92
APOE ε4 carriers	1.28	0.99; 1.66	0.06	1.37	1.05; 1.78	0.02

HR and 95% CI estimated using a Cox proportional hazards model with follow-up time (years) as the time scale. To facilitate interpretation of identified interactions between dietary patterns and APOE ε4 in relation to incident dementia, separate effect values for the prediction scores are shown for APOE ε4 carriers and APOE ε4 non-carriers.

[a]*Model 1 is adjusted for sex and birth year. Model 2 is adjusted for sex, birth year, BMI, energy intake, total cholesterol level, hypertension, diabetes, physical activity level, educational level, and smoking and five principal components (PCs) to correct for population stratification.*

[b]*Dementia events/total cases. Those with missing data were excluded in model 2 (n=29 with missing data, n=5 for BMI, n=3 for serum cholesterol, n=5 for education, n=10 for physical activity level and n=7 for smoking).*

Source: Table 6 in Samuelsson et al. 2021 (188).

4.4 PAPER IV

Samuelsson J, Marseglia A, Lindberg O, Westman E, Kern S, Ahlner F, Rothenberg E, Skoog I, Zettergren A. **Associations between dietary patterns and markers of neurodegeneration and cerebrovascular pathology: a population-based study.** Manuscript.

This manuscript has not been published but there will be a short summery of the main results from paper IV in this section.

Comparisons in characteristics between men and women showed that women had a higher adherence to the MeDi-like pattern compared to men, and men had a higher energy intake, and higher adherence to the western and low-fiber/high-alcohol pattern compared to women. Men had lower total mean cortical thickness, less white matter microstructural integrity (DTI measures), more participants with a SVD score of 0 (low SVD burden) compared to women. There was no difference in mean AD-signature cortical thickness, MMSE score, BMI, smoking status, physical activity and educational level between men and women.

The main findings were that higher adherence to a low-fiber/high-alcohol dietary pattern was negatively associated with cortical thickness in the whole brain and with the AD cortical signature. These findings remained in subgroup-analyses were those with the highest alcohol intake were removed. There was a positive association between a Mediterranean-like dietary pattern and better white matter microstructural integrity. However, no associations were found between the dietary patterns and a global SVD score or hippocampal volume. Nor could we find any associations between a western dietary pattern and the MRI markers.

5 DISCUSSION

Epidemiologic studies are essential to identify determinants or causes of disease, and for estimating the prevalence of diseases in a population. This is especially important for the prevention of diseases such as sporadic AD, where the disease progression is long, and where several determinants can affect disease risk and development. However, epidemiological studies are challenging to perform and requires several considerations to minimize bias such as selection and information bias. This chapter contains methodological discussions on the dietary examination, on the construction of dietary patterns, and on papers I – IV, followed by summarizing chapters of strengths and limitations and a general discussion.

5.1 METHODOLOGICAL DISCUSSION

Dietary examination

Reporting and recall biases are important factors to consider in nutritional epidemiology since dietary assessment methods usually are retrospective and based on self-reported dietary intake (203). The most common method to examine dietary intake in large-scale epidemiological studies is with self-administered retrospective food frequency questionnaires (FFQs). An FFQ is a quick and inexpensive method that is designed to estimate habitual food intake (usually covering the preceding 6-12 months) of selected foods (203). An FFQ mainly investigate frequencies, but the methods accuracy in measuring food, energy and nutrient intake can be improved by including portion size assessments (e.g., by predetermined portion sizes) (204). However, an FFQ needs to capture foods consumed in the population that is being examined, which can be challenging with the increase in foods available. Other commonly used dietary assessment methods are retrospective 24-h recall interviews (the participant is interviewed about what they consumed the past 24 hours), and prospective food records, where the participants register their dietary intake per day in a food diary (usually for 3 – 7 days) (203, 205). Food diaries may capture daily intake well if reported accurately, but food diaries have the downside of usually just capturing a few days intake (e.g., missing foods not eaten regularly). This is true also for the 24-h recall method, that needs to be repeated to cover more than one day intake. Also, these methods all rely on the participants willingness and ability to report their dietary intake accurately. The retrospective methods all rely on memory, which can be problematic when investigating dietary intake among populations where memory impairments are more common (e.g., among older adults). The Diet

history (DH) method used in the H70-studies is a retrospective dietary assessment method that relies on recall and the ability to report frequencies and portion sizes of foods consumed. The diet history method was first described in 1947 by Burke (206). It originally contained a meal-pattern interview, a list of questions on usual frequencies and portion sizes of foods and a 3-day diet record. The method has been modified over the years and exists nowadays in a variety of versions (203). In the H70 studies, the DH method included a meal-pattern interview where the participants described their meal-pattern for a regular day (from first to last meal, including snacks and beverages), and if/how a regular day differed from a day during the weekend, followed by questions on usual frequencies and portion sizes of foods and beverages consumed the preceding three months. The meal-pattern report (including regularly consumed foods/beverages) was used as a checklist during the interview to make sure that foods eaten regularly would not be missed when more detailed questions on frequencies and portion sizes of foods and beverages were asked, thus increasing the possibility of measuring habitual intake accurately. Measuring dietary intake for the preceding three months may also capture foods/beverages not regularly consumed. However, seasonal effects on dietary intake may have been missed. Compared to an FFQ, the H70 DH method has the advantage of measuring dietary intake at a very detailed level (e.g., brand of bread, type of vegetable, meat/meat product), and portion sizes are individualized since the participant estimates portion sizes based on pictures of foods or measurements (e.g., glass, cup, table spoon etc.). The DH method in the H70-studies has been slightly modified between birth cohorts to capture the increasing variety of foods available.

Misreporting of dietary intake can occur independently of dietary assessment method (203). The content of the food/nutrient database, the participants ability to interact with the dietary assessment tools, and interactions between interviewer and the interviewee, are factors that may influence the degree of misreporting (203). The risk of misreporting dietary intake may have been diminished in the H70 studies by having trained registered dietitians performing the interviews, and by using the Swedish NFAs database that includes detailed properties of more than 2000 foods and dishes. However, misreporting of energy intake is common in studies investigating dietary intake, especially underreporting of energy intake (203, 207). EI/BMR values can be used to estimate potential underreporting of energy intake based on the theory that EI/BMR should equal PAL (185). A PAL value of 1.35*BMR has been considered the minimum energy expenditure compatible with a normal active lifestyle (208). In paper I, the mean EI/BMR was above the 1.35 cut-off set to detect potential underreporting of energy intake during the study period (1971 – 2016) (176). However, there were participants with an EI/BMR below

1.35 at all examinations, indicating some underreporting of energy intake (176). A previous H70 study found that the DH method used in the dietary examinations underestimated energy intake with 12 % when compared with the double labelled water method (an isotope-based technique for assessing energy expenditure) (179). Underreporting of energy intake has been associated with overweight and obesity, whereas reporting a high energy intake has been associated with a low BMI (207). In paper I, we found negative correlations between EI/BMR and BMI at all examinations during the study period (1971 – 2016), indicating that underreporting of energy intake was more common among those with a higher BMI at all examinations (176). Some low reports on energy intake may however been caused by a reduced dietary intake (e.g., being on a diet, or disease-related). In paper I, subgroup analyses were performed on macro- and micronutrient intake excluding those with an EI/BMR < 1.35. These analyses showed similar linear trends as those performed on the total population.

The DH interview is not as common as an FFQ in epidemiological studies. The DH method is time-consuming and expensive, which may limit the use, especially in large-scale epidemiological studies. The dietary examinations between 1971 – 1993 were performed on a subsample, which limits representativeness. In the 2000-02 examination the dietary interview was included in the general examination, resulting in a high participation rate in the dietary examination (92 %). The dietary examination was an additional examination in the 2014-16 examination, which may explain why the participation rate in the 2014-16 dietary examination (72 %) was lower than in 2000-02. However, the dietary examination in 2014-16 still had the largest number of participants compared to previous examinations in the H70 studies. The larger sample sizes in the 2000-02 and 2014-16 dietary examinations were positive, since larger sample sizes may reduce the effect of random errors. The DH method was used at all examinations to ensure comparability between birth cohorts.

Dietary patterns

Studies that explore the impact of dietary patterns on incident dementia are needed to increase the understanding of food and nutrient compositions that may prevent or delay the onset of dementia. There are a several different ways to derive dietary patterns, such as a priori (e.g., dietary quality scores), posteriori (e.g., PCA), and a combination of a priori and posteriori approaches, such as the RRR (209-211). Choosing the best approach is always difficult since there are advantages and disadvantages with most methods (211). A priori methods, such as a dietary index, may be useful for investigating

adherence to a specific diet (e.g., a MeDi index, common in dementia research), but has the drawback of generally not reflecting overall diet (211). Posteriori approaches such as the PCA can be used to describe food patterns in a population (209). A PCA is a data-driven exploratory approach to derive dietary patterns (based on uncorrelated principal components) that relies on inter-correlations among dietary variables (i.e., food groups) (211). Using a PCA to derive dietary patterns may provide new information about food combinations that could be associated with dementia or dementia-related factors, but a PCA may also derive patterns that are not related to the outcome (the model does not consider previous knowledge about dietary factors that have been associated with dementia). We chose to derive dietary patterns with PCA in paper II and IV since results from previous studies investigating associations between dietary patterns and CSF/MRI biomarkers related to AD and dementia were inconclusive, and since there were few studies that investigated associations with other dietary patterns than the MeDi. In paper III, we chose the RRR method to derive dietary patterns since we wanted to use an exploratory approach that also considers previous knowledge about dietary factors associated with incident dementia (211). Including information on nutrient intake in the derivation of dietary patterns can provide insights on risk reducing or risk increasing components of different dietary patterns. The RRR is a multivariate analysis that considers multicollinearity in both the response (i.e., nutrients) and predictor (i.e., food groups) variables. We are aware that we have chosen some out of several nutrients that have been associated with incident dementia. The response variables were selected based on previous literature as having a "stronger" evidence base in modifying the risk of developing dementia (114). We could not include polyphenols since we did not have the data, and we chose to not include vitamin D since the sun is a contributing factor (there was no data on vitamin D status available).

The naming of the dietary patterns in papers II – IV was a way to simplify presenting and discussing the results. Dietary patterns that exist in a population are seldom strictly either healthy or not healthy, but we chose labels for the dietary patterns that reflected overall intake/main components. However, the dietary patterns, and the labels we chose for them, should be put in the context of a Swedish dietary pattern and the similarities to MeDi and western dietary patterns are relative to the dietary pattern of the populations in question.

Paper I

Paper I is a descriptive paper that investigated time trends in energy, macro- and micronutrients, foods (mean gram/day and the proportion participants that consumed these foods), the proportion of participants at risk of and inadequate

intake of certain micronutrients, the proportion of participants with a higher alcohol intake then recommended by NNR 2012, and the distribution of E % from macronutrients and alcohol, with comparisons to the NNR 2012 (176). In paper I, we used data from five cross-sectional studies examined between 1971 – 2016. The cross-sectional study design is suitable when the aim is to perform a descriptive study. However, longitudinal follow-ups in dietary intake would have provided valuable insights on potential changes in dietary patterns within each birth cohort. Despite the cross-sectional design, some of the results were presented as an increase/decrease. This was done to simplify presentation and discussion of the results.

Paper II

Paper II is a cross-sectional study that investigated associations between dietary patterns derived by PCA and AD hallmark CSF biomarkers (187). The cross-sectional design limits the possibility to draw conclusions about causality since it does not reflect directionality of the association, or previous exposures. The associations were investigated with linear and logistic regression models, which allow adjustment for confounders that may influence the association between the dietary patterns and the outcome. The confounders were chosen a priori based on previous literature. However, there could be other confounding factors that we did not include. In paper II, we chose to limit the number of confounders due to the exploratory approach of the study, and to not overfit the models (especially the binary logistic regression models).

The participation rate in the CSF examination was lower than for the other examinations in the 2014-16 examination (169). An LP can be perceived as an invasive examination, which is most likely the reason for the lower response rate in this examination (36 %). Contraindications to perform and LP, and lack of dietary data among some of the participants in the CSF sample, reduced the sample size further in paper II (22 % of the total sample). A previous study investigating the CSF sample from the 2014-16 examination found that the prevalence of pathological AD markers was common (46 %) (177). This led us to believe that associations could be investigated even though the sample size was reduced. The CSF sample also seemed to be representative of the total sample in the 2014-16 examination (177).

Even though the sample size is small in comparison to the total sample, it is still relatively large in comparison to other studies investigating associations between diet and AD hallmark CSF biomarkers (152). However, there may still be an issue of low statistical power in some of the analyses where the

number of participants with pathological levels were few (e.g., p-tau pathology).

Paper III

Paper III is a prospective cohort study that investigated gene-dietary pattern interactions among 70-year-olds in relation to incident dementia (188). We explored these associations with Cox regression models. The Cox (proportional hazards) regression is a survival analysis that considers time to an event (i.e., dementia) and censorship (i.e., death, attrition). To reduce the issue of having to censor because of attrition (common in longitudinal studies), we used registry data on death and dementia to extend the follow-up time for those that were lost to follow-up. The prospective study design of paper III increases the possibility to draw conclusions on causality.

Determining the prevalence of dementia in a population can be affected by the criteria used to diagnose dementia. This was shown in a previous paper from the H70 studies where the prevalence of dementia ranged between 1.2 % and 9.6 % depending on the criteria used (i.e., DSM-III-R, DSM-IV, "historical criteria", ICD-10, and ICD-9) (212). The prevalence was 3.1 % according to ICD-10, 6.3 % according to DSM-III-R, and 9.6 % according to DSM-IV criteria (212). The difference in prevalence by following DSM-III-R criteria compared to DSM-V was mainly explained by the requirement of both long-term and short-term memory in DSM-III-R (212). In paper II – IV, dementia was diagnosed according to DSM-III-R criteria. However, the criteria used were less strict and more like DSM-IV in the aspect that either long- or short-time memory was required, not both. In paper III, the registry data used to reduce censorship due to attrition were based on information from the NPR (ICD-10 criteria were used to diagnose dementia) (213). Even though the NPR may have criteria that are less sensitive in detecting dementia cases, the NPR still cover most patients that receive care within public health care in Sweden (214).

Blood sampling for the genetic analyses were performed in 2000-02, also for the participants in the 1992-93 examination. This may have led to a certain selection bias since the participants from the 1992-93 dietary examination that were lost to follow-up, or had died before the re-examination in 2000-02, had to be excluded. Also, there were no men with genotype data in the 1992-93 examination.

The statistical power to detect interactions may be lower than for main effects (a larger sample size may be needed to detect an interaction compared to main

effect associations) (215). To decrease the risk of incorrectly concluding that there were no interaction effects, we raised the *p*-value threshold for potential interactions to 0.1. This could be considered arbitrary, but to be comparable with other studies in this field, we chose a *p*-value threshold of < 0.1 (216-218).

Some of the potential confounders, such as hypertension, diabetes, and total cholesterol, may potentially be mediators. However, including them did not alter the results.

There may have been an issue of power in the models including the non-*APOE* AD-PRSs analyses since associations may be harder to detect due to the weaker risk modifying effects on AD compared to *APOE ε4* (99). Also, the outcome variable was dementia, which could include other subtypes than AD (subtypes with a weaker link to the genetic risk factors). This may have attenuated the results. Dementia subtypes were not available for the 2015-16 examination and could therefore not be investigated in paper III.

Paper IV

Paper IV is a cross-sectional study that explored associations between dietary patterns and neuroimaging markers related to dementia. The cross-sectional study design, selection process of confounders, and statistical analyses were similar to paper II, discussed above in the section for paper II.

A previous study examining the MRI sample in the 2014-16 examination found some differences in characteristics between those that took part of the MRI examination (66 %) and those that did not (219). Those who participated had higher educational level (88 % vs 80 % with an educational level > mandatory), were more often non-smokers (12 % vs. 8 %), had a higher mean MMSE score (29 vs. 30), and had less often dementia (2 % vs. 4 %) (219). However, no differences were found between participants and non-participants regarding alcohol risk consumption, BMI, blood pressure, *APOE ε4* status, atrial fibrillation, and cardiovascular-related conditions (e.g., atrial fibrillation, heart failure) (219).

The main results from the cortical thickness analyses were based on the analyses that included mean cortical thickness as a marker of overall neurodegeneration, and an AD-signature cortical thickness marker derived by averaging cortical thickness of AD-signature regions (entorhinal, inferior temporal, middle temporal, and fusiform regions from the Desikan Atlas) (77). However, we chose to also include whole-brain surface-based analyses that

explored potential associations between the dietary patterns and cortical thickness in the left and right hemispheres in an unbiased way. These analyses were added for descriptive purposes, and were only adjusted for sex.

The dietary patterns in paper II and IV were similar since they were both derived from the dietary sample in the 2014-16 examination. However, there were a few differences in the construction of the patterns between the two papers. In paper IV there were 27 food groups included in the PCA compared to the 22 food groups in paper II. In paper II, some of the food groups included in paper IV were comprised into a larger food group containing foods with similar nutritional properties. In paper IV we wanted to explore if a more detailed inclusion of these food groups would affect the composition of the patterns. The food group "sweets" in paper II contained the food groups "sweet bakery", "desserts", "sweet condiment" and "sweets/candy/chocolate" that were included as separate food groups in paper IV. "Alcoholic beverages" in paper II were divided into "wine" and "other alcoholic beverages" in paper IV. In paper II, we did not include the food group "snacks" (e.g., chips, popcorn) since a large proportion reported that they did not consume snacks. In paper IV, we included "snacks" in the "fast food/savory bakery category". These changes did not affect the composition of the three components (dietary patterns) that explained most of the variation much. However, to describe the overall content, we chose to label two out of the three dietary patterns slightly different in paper IV.

5.1.2 STRENGTHS IN SUMMARY

There are several strengths with the papers included in this thesis. First, the systematically selected population-based samples, and the high response rates in the H70 studies have provided representative samples of the general population. Other strengths were the comprehensive examinations, the multidisciplinary approach including trained and specialized research staff performing the interviews, health examinations and diagnostics. The long follow-up time for incident dementia in paper III, and the possibility to explore dietary intake among five birth cohorts of 70-year-olds over the past five decades were unique. Strengths with the dietary examinations were that the diet history interviews were performed by registered dietitians, and that the method provided detailed information on habitual dietary intake. Strengths regarding the outcome variables of paper II – IV were 1.) that the ability to identify and diagnose dementia following established diagnostic criteria was possible due several sources of information, 2.) that the CSF sample was relatively large compared to other studies, and included both Aβ and tau biomarkers 3.) that the MRI data included several markers of neurodegeneration and cerebrovascular pathology, including DTI data on microstructural white matter integrity.

5.1.3 LIMITATIONS IN SUMMARY

There were also methodological limitations. The sample sizes included in this thesis (i.e., sample sizes for individuals with data on diet and biomarkers) were lower than for the general examinations due to factors such as lower participations rates in the additional examinations, that some of the examinations were performed on subsamples, and that some examinations could be considered invasive. This may have affected the representativeness and statistical power of some of the analyses. Recall and misreporting of dietary intake are common in epidemiological studies investigating dietary intake in a population. This is most likely true for the H70 studies as well, even though the dietary examination method including face-to-face interviews performed by a dietitian may have limited this methodological issue. Paper II and IV provides insights on potential associations between dietary patterns and biomarkers related to dementia that has not/seldom been investigated in previous studies, but the cross-sectional design limits the possibility to draw conclusions on causality. In paper III, there was only dietary data available from the baseline examination. The analyses do thereby not consider potential effects of dietary intake before the age of 70 years, or potential changes in dietary intake during the study period. All the papers in this study include dietary data on Swedish 70-year-olds, which may limit generalizability.

5.2 GENERAL DISCUSSION

The results from paper I showed that the intake of several healthy foods increased among 70-year-olds over time, and that the intake was highest among the 70-year-olds examined in 2014-16. In previous studies among older adults, healthier dietary patterns have been associated with higher physical activity level, higher educational level, non-smoking, and being married (22, 27-30). In paper I, we did not explore these associations, but comparisons between birth cohorts showed that 70-year-olds were more physically active, had higher educational level, were more often non-smokers (especially among men), and more often married/cohabiting (among women) in the 1944 birth cohort compared to previous born birth cohorts. The time trend towards higher intakes of alcohol may be related to a more "continental" lifestyle with wine/beer accompanying the main meal. In paper II and IV, we found a dietary pattern (the high-alcohol dietary pattern) in the 1944 birth cohort that supports this notion. Even though this is not a healthy trend, there may be a "quality of life" aspect associated with the higher alcohol intake in the latest born birth cohort. Previous studies investigating dietary patterns among European countries between the late 1980s and early 2000, found overall healthier dietary patterns among southern European countries compared to northern European countries (29, 30). Compared to those studies, dietary intake in the 2014-16 examination (e.g., higher intake of vegetables, pulses, fruits, and fish) corresponded more to the dietary patterns found in the southern European countries than to the patterns found in the northern European countries (29, 30). Results from paper I were in line with the NFA surveys on dietary intake in the Swedish adult population (between 1989 – 2011), as well as trends seen in the neighboring Finnish population between 1985 – 2000 (24, 28). Mean BMI were between 26 – 27 (overweight category) among the participants that took part in the dietary examinations between 1971 – 2016. Overweight has not been associated with an increased risk of mortality among older adults, while a lower BMI (< 23) has (220).

In paper I, results indicate that 70-year-olds follow food-related trends in the society. The decreased intake of milk products in the 2014-16 examination was in line with the decreased consumption of milk products in Sweden (221). Further, the trend towards a decrease in low-fat milk products, refined bread and sweet bakery and the increased intake of cream/crème fraiche and cheese in the 2014-16 examination may have been influenced by the trend of eating low-carbohydrate/high-fat diets that was highly promoted in media around that time. Also, the trend towards an increased consumption of fish/seafood, vegetables/pulses, fruits/berries, nuts/seeds, and wholegrain products such as fiber-rich bread, could indicate an awareness of healthy dietary guidelines in

the later born birth cohorts. The time trend towards overall healthier dietary choices may also have been influenced by the increased availability and variety of healthy foods, by a relative decrease in food prices, and by an increase in socio-economic standard between 1971 – 2016 (221).

Previous studies have found either no relations between dietary patterns and incident dementia, reduced dementia risk with healthy MeDi-like dietary patterns, or increased risk with western-like dietary patterns (114, 118, 123). Whether genetic predisposition modifies the impact of dietary patterns on dementia risk has not been established. There are previous studies that have investigated interactions between genetic factors and either nutrients, single foods, or dietary patterns, in relation to cognitive tests or dementia, but results are inconclusive, and few studies have investigated gene-dietary pattern interactions in relation to incident dementia (126, 134, 216, 222-224). In paper III, we found no associations between either a healthy or a western dietary pattern in relation to incident dementia among 70-year-olds that were followed for in average 13 years, when genetic predisposition was not considered (188). However, we found interactions between the dietary patterns and *APOE ε4* (carrier/non-carrier) in relation to incident dementia, indicating that genetic risk may modify the impact of dietary patterns on dementia risk. A potential explanation can be that dietary factors and genetic factors may act synergistically if pathways are shared (e.g., pathways concerning hypercholesterolemia, hypertriglyceridemia, increased insulin resistance, enhanced response to inflammation and atherosclerosis) (94, 167). Unexplored interactions between dietary patterns and *APOE ε4* status may provide one explanation to inconclusive results from previous studies investigating dietary patterns in relation to incident dementia.

Paper III was to our knowledge the first paper that investigated interactions between dietary patterns and non-*APOE* AD-PRSs in relation to incident dementia. We could not find any interactions between the dietary patterns and the non-*APOE* AD-PRSs in relation to incident dementia. Neither could another study (published after paper III) that investigated interactions between the MIND diet and non-*APOE* AD-PRSs in relation to incident dementia and cognitive decline among three US cohorts (≥ 65 years from the Chicago Health and Aging Project (n = 2449), Rush Memory and Aging Project (n = 725), and Women's Health Initiative Memory Study (n = 5308) (225).

Previous studies investigating associations between diet and AD hallmark biomarkers differs in study design (e.g., CSF biomarkers/PET biomarkers, differences in age, cognitive status, nutrients/single foods, or dietary patterns), which may explain inconsistencies in results (152). Most previous studies

investigating dietary patterns in relation to AD hallmark biomarkers explored associations between MeDi-like dietary patterns and Aβ burden measured with PET (153-158, 160, 161). These studies found either no associations (160, 161), or less Aβ burden with higher adherence to MeDi-like patterns (153-158). One study that investigated dietary patterns derived by PCA in relation to Aβ burden measured with PET, found no associations with a MeDi-like pattern, but did find an association between higher adherence to a "junk food" dietary pattern and more Aβ burden (160). In paper II, the main AD-related finding was the association between higher adherence to a western dietary pattern and pre-clinical AD (i.e., Aβ42 and tau pathology) (187). It has been suggested that disruptions in the homeostasis of lipid and glucose metabolism and inflammatory processes may be involved in production and clearance of Aβ and tau phosphorylation (147, 150). Theoretically, the western dietary pattern may promote these processes and thereby provide a potential explanation for the association between higher adherence to the western dietary pattern and pre-clinical AD found in paper II. However, results from paper II should be interpreted with caution and be further investigated in studies with a longitudinal approach.

Previous studies have investigated associations between dietary patterns and dementia-related MRI markers, but results are inconclusive (162-166). Moreover, previous studies mainly explored associations between MeDi-like patterns and brain MRI markers (162, 163), thereby limiting comparisons with results from paper IV. In paper IV, we found associations between a low-fiber/high-alcohol dietary pattern and overall thinner cortical thickness (marker of neurodegeneration), and thinner cortical thickness in AD-specific regions. However, the association with the AD-specific regions was less precise in the model that was only adjusted for sex. Also, the whole-brain surface-based unbiased analyses indicate associations with regions that may not be AD specific. We found no other studies that investigated associations between a dietary pattern similar to the low-fiber/high-alcohol pattern and brain MRI markers. However, since alcohol may be a driving factor between these associations, we chose to perform a sensitivity analysis where those with the highest alcohol intake were removed. The results remained, which indicates that even a low to moderate alcohol intake may have a negative impact, as shown in a previous study investigating alcohol consumption and brain outcomes (grey matter density, hippocampal atrophy, and white matter microstructural integrity) (226), or that alcohol may not be the only factor in the dietary pattern that drives the association. The positive association between the MeDi-like pattern and white matter microstructural integrity indicates an association with early cerebrovascular alterations that may not yet be detectable with the SVD score.

6 CONCLUSION

Exploring dietary intake and dietary patterns among older adults can provide insights into whether health promoting dietary guidelines are followed and if nutrient needs are met. Results from paper I showed that dietary patterns changed between 1971 – 2016, with an increase in healthy foods such as vegetables/pulses, fruits/berries, fish/shellfish, nuts/seeds, and wholegrain products. There was also an increase in protein intake and a decrease in the proportion 70-year-olds at risk of an inadequate intake of certain vitamins and minerals. However, there were still more than 30 % of the men and almost 50 % of the women at risk of an inadequate vitamin D intake from diet, and about 30 % of both men and women had a protein intake below the lowest recommended level of gram protein/kg body weight/day in the latest born birth cohort examined 2014-16. Also, more than 30 % had an alcohol intake above the upper daily intake level recommended in the NNR 2012, in the 2014-16 examination. Further, results from paper I indicates that 70-year-olds in the latest born birth cohort follow societal food-trends and dietary guidelines. Results from paper I can be useful as a basis for dietary guidelines and prevention strategies to promote healthy ageing among older adults.

Diet is a lifestyle factor that may modify the risk of dementia. This thesis contributes with insights on associations between dietary patterns and biomarkers related to dementia, which have seldom, or never, been investigated previously, and insights on gene-dietary pattern interactions that may modify the risk of dementia. In paper III, we found interactions between *APOE ε4* status and dietary patterns in relation to incident dementia. The results showed that a higher adherence to a healthy dietary pattern reduced the risk of dementia among *APOE ε4* non-carriers, but not among *APOE ε4* carriers. On the other hand, *APOE ε4* carriers with a higher adherence to a less healthy western dietary pattern had an increased risk of dementia that was not seen among *APOE ε4* non-carriers. To our knowledge, paper III is the first study to investigate interactions between dietary patterns and non-*APOE* AD-PRSs in relation to incident dementia. We could not find any interactions between the dietary patterns and four non-*APOE* AD-PRSs in relation to incident dementia. Also, we could not find any associations between the dietary patterns and incident dementia when gene-dietary pattern interactions were not considered. The results from paper III indicate that *APOE ε4* status could modify the impact of dietary patterns on the risk of developing dementia, and that *APOE ε4* status should be considered in studies investigating associations between dietary patterns and incident dementia. In paper II and IV, we found cross-sectional associations between three dietary patterns and

CSF AD hallmark biomarkers, and dementia-related brain MRI markers of neurodegenerative and vascular pathology. In paper II, a higher adherence to a western dietary pattern was associated with t-tau pathology (a marker of neurodegeneration) and pre-clinical AD (a combination of Aβ and tau pathology, but no apparent symptoms). Results from paper IV showed negative associations between adherence to a low-fiber/high-alcohol dietary pattern and MRI markers of general and AD-specific neurodegeneration (cortical thickness measures). Further, positive associations were found between adherence to a MeDi-like pattern and more white matter microstructural integrity. Results from paper II and IV provide valuable insights on dietary patterns that potentially could modify the risk of dementia through neurodegenerative and cerebrovascular pathways. These insights can be used, and investigated further, in longitudinal and intervention studies to enable precision nutrition in dementia prevention strategies.

7 FUTURE PERSPECTIVES

Diet is a modifiable lifestyle factor that could impact the risk of developing dementia. However, additional studies are needed to enable precision nutrition in dementia prevention strategies. Prospective cohort studies and intervention studies investigating the impact of dietary patterns on the risk of developing dementia are needed to establish risk modifying effects of diet on dementia. Future studies should explore dietary patterns that cover overall dietary intake to increase the knowledge about food combinations that synergistically could modify dementia risk. There is also a need for studies that investigate associations between dietary patterns and potential pathways linking diet with dementia (e.g., vascular, inflammatory, neurodegenerative), as well as studies that investigate the impact of dietary patterns on markers related to AD and incident dementia at different ages in life. Further, studies investigating interactions between dietary patterns and *APOE* status and non-*APOE* AD-PRSs in relation to incident dementia are wanted to confirm the results from this thesis.

Future H70 studies would benefit from including a dietary examination at all follow-up examinations to explore potential changes in dietary intake, and effects of diet on health, in an ageing population. Additional measuring points of dietary intake could also provide knowledge about the impact of dietary patterns on the disease progression for diseases such as AD at different ages.

Even though there are limitations with most dietary examination methods in epidemiological studies, they still provide valuable insights on dietary intake on a population level. In future studies, food-derived biomarkers (e.g., from blood or urine) could be used as a complement to traditional dietary examination methods, for validation, and as markers on dietary intake, to reduce the risk of measurement errors that may affect analyses and the interpretation of results.

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REFERENCES

1. United Nations. Department of Economic and Social Affairs, Population Division (2019). World Population Prospects 2019: Highlights (ST/ESA/SER.A/423).
2. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). 2018;392(10159):1684-735.
3. Mackenbach JP, Looman CW. Living standards and mortality in the European Community. J Epidemiol Community Health. 1994;48(2):140-5.
4. Marmot M, Friel S, Bell R, Houweling TA, Taylor S. Closing the gap in a generation: health equity through action on the social determinants of health. Lancet (London, England). 2008;372(9650):1661-9.
5. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. Nature. 2019;571(7764):183-92.
6. Vetrano DL, Palmer K, Marengoni A, Marzetti E, Lattanzio F, Roller-Wirnsberger R, et al. Frailty and Multimorbidity: A Systematic Review and Meta-analysis. J Gerontol A Biol Sci Med Sci. 2019;74(5):659-66.
7. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev. 2011;10(4):430-9.
8. Salomon JA, Wang H, Freeman MK, Vos T, Flaxman AD, Lopez AD, et al. Healthy life expectancy for 187 countries, 1990-2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet (London, England). 2012;380(9859):2144-62.
9. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet (London, England). 2015;385(9967):549-62.
10. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). 2019;393(10184):1958-72.
11. Vergnaud AC, Romaguera D, Peeters PH, van Gils CH, Chan DS, Romieu I, et al. Adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines and risk of death in Europe: results from the European Prospective Investigation into Nutrition and Cancer cohort study1,4. Am J Clin Nutr. 2013;97(5):1107-20.
12. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413-46.

13. Institute for Health Metrics and Evaluation (IHME). Results from the 2019 Global Burden of Disease (GBD) Study. https://vizhub.healthdata.org/gbd-compare/; 2019.
14. Swedish Food Agency. The Swedish dietary guidelines. https://www.livsmedelsverket.se/en/food-habits-health-and-environment/dietary-guidelines/adults; 2022.
15. Nordic Council of Ministers. Nordic Nutrition Recommendations 2012: Integrating nutrition and physical activity. https://norden.diva-portal.org/smash/get/diva2:704251/FULLTEXT01.pdf; 2012.
16. Christensen JJ, Arnesen EK, Andersen R, Eneroth H, Erkkola M, Høyer A, et al. The Nordic Nutrition Recommendations 2022 - principles and methodologies. Food Nutr Res. 2020;64:10.29219/fnr.v64.4402.
17. Herforth A, Arimond M, Álvarez-Sánchez C, Coates J, Christianson K, Muehlhoff E. A Global Review of Food-Based Dietary Guidelines. Advances in nutrition (Bethesda, Md). 2019;10(4):590-605.
18. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clin Nutr. 2019;38(1):1-9.
19. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing. 2014;43(6):748-59.
20. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc. 2013;14(8):542-59.
21. Remelli F, Vitali A, Zurlo A, Volpato S. Vitamin D Deficiency and Sarcopenia in Older Persons. Nutrients. 2019;11(12).
22. Poggiogalle E, Kiesswetter E, Romano M, Saba A, Sinesio F, Polito A, et al. Psychosocial and cultural determinants of dietary intake in community-dwelling older adults: A Determinants of Diet and Physical Activity systematic literature review. Nutrition. 2021;85:111131.
23. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr. 2019;38(1):10-47.
24. Amcoff E, Edberg A, Barbieri HE, Lindroos AK, Nälsén C, Pearson M, Lemming EW. Riksmaten-vuxna 2010–11. Livsmedels- och näringsintag bland vuxna i Sverige (Riksmaten-adults 2010–11. Food and Nutrient Intake Among Adults in Sweden). Uppsala: Livsmedelsverket; https://www.livsmedelsverket.se/globalassets/publikationsdatabas/rapporter/2011/riksmaten_2010_20111.pdf; 2012.
25. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol. 2007;17(9):643-53.

26. Eiben G, Andersson CS, Rothenberg E, Sundh V, Steen B, Lissner L. Secular trends in diet among elderly Swedes -- cohort comparisons over three decades. Public Health Nutr. 2004;7(5):637-44.
27. Cabrera C, Rothenberg E, Eriksson BG, Wedel H, Eiben G, Steen B, et al. Socio-economic gradient in food selection and diet quality among 70-year olds. J Nutr Health Aging. 2007;11(6):466-73.
28. Sulander T, Helakorpi S, Rahkonen O, Nissinen A, Uutela A. Changes and associations in healthy diet among the Finnish elderly, 1985-2001. Age Ageing. 2003;32(4):394-400.
29. Haveman-Nies A, Tucker KL, de Groot LC, Wilson PW, van Staveren WA. Evaluation of dietary quality in relationship to nutritional and lifestyle factors in elderly people of the US Framingham Heart Study and the European SENECA study. Eur J Clin Nutr. 2001;55(10):870-80.
30. Bamia C, Orfanos P, Ferrari P, Overvad K, Hundborg HH, Tjønneland A, et al. Dietary patterns among older Europeans: the EPIC-Elderly study. Br J Nutr. 2005;94(1):100-13.
31. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(1):88-106.
32. Patterson C. Alzheimer's Disease International; London: 2018. World Alzheimer report 2018.
33. Wu YT, Beiser AS, Breteler MMB, Fratiglioni L, Helmer C, Hendrie HC, et al. The changing prevalence and incidence of dementia over time - current evidence. Nature reviews Neurology. 2017;13(6):327-39.
34. Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimers Res Ther. 2016;8(1):23.
35. Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States: The Alzheimer Cohorts Consortium. Neurology. 2020;95(5):e519-e31.
36. Larson EB, Yaffe K, Langa KM. New insights into the dementia epidemic. N Engl J Med. 2013;369(24):2275-7.
37. Licher S, Heshmatollah A, van der Willik KD, Stricker BHC, Ruiter R, de Roos EW, et al. Lifetime risk and multimorbidity of non-communicable diseases and disease-free life expectancy in the general population: A population-based cohort study. PLoS Med. 2019;16(2):e1002741.
38. Gale SA, Acar D, Daffner KR. Dementia. Am J Med. 2018;131(10):1161-9.
39. O'Brien JT, Thomas A. Vascular dementia. Lancet (London, England). 2015;386(10004):1698-706.
40. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet (London, England). 2006;368(9533):387-403.
41. 2022 Alzheimer's disease facts and figures. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2022;18(4):700-89.

42. Wolters FJ, Ikram MA. Epidemiology of Vascular Dementia. Arterioscler Thromb Vasc Biol. 2019;39(8):1542-9.
43. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer's disease. Lancet (London, England). 2021;397(10284):1577-90.
44. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992;256(5054):184-5.
45. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-6.
46. Jack CR, Jr., Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-16.
47. Crimins JL, Pooler A, Polydoro M, Luebke JI, Spires-Jones TL. The intersection of amyloid β and tau in glutamatergic synaptic dysfunction and collapse in Alzheimer's disease. Ageing Res Rev. 2013;12(3):757-63.
48. Veitch DP, Weiner MW, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. Understanding disease progression and improving Alzheimer's disease clinical trials: Recent highlights from the Alzheimer's Disease Neuroimaging Initiative. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2019;15(1):106-52.
49. Braak H, Zetterberg H, Del Tredici K, Blennow K. Intraneuronal tau aggregation precedes diffuse plaque deposition, but amyloid-β changes occur before increases of tau in cerebrospinal fluid. Acta Neuropathol. 2013;126(5):631-41.
50. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci. 2004;5(5):347-60.
51. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2016;12(3):292-323.
52. Cacace R, Sleegers K, Van Broeckhoven C. Molecular genetics of early-onset Alzheimer's disease revisited. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2016;12(6):733-48.
53. Nardini E, Hogan R, Flamier A, Bernier G. Alzheimer's disease: a tale of two diseases? Neural Regen Res. 2021;16(10):1958-64.
54. Bir SC, Khan MW, Javalkar V, Toledo EG, Kelley RE. Emerging Concepts in Vascular Dementia: A Review. J Stroke Cerebrovasc Dis. 2021;30(8):105864.
55. Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. Neurobiol Aging. 2000;21(2):321-30.
56. van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH, et al. Vascular cognitive impairment. Nat Rev Dis Primers. 2018;4:18003.

57. Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet (London, England). 2015;386(10004):1672-82.
58. Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. Lancet (London, England). 2015;386(10004):1683-97.
59. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. Int Rev Psychiatry. 2013;25(2):130-7.
60. Spence JD. Metabolic vitamin B12 deficiency: a missed opportunity to prevent dementia and stroke. Nutr Res. 2016;36(2):109-16.
61. Rehm J, Hasan OSM, Black SE, Shield KD, Schwarzinger M. Alcohol use and dementia: a systematic scoping review. Alzheimers Res Ther. 2019;11(1):1.
62. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614-29.
63. Sorbi S, Hort J, Erkinjuntti T, Fladby T, Gainotti G, Gurvit H, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurol. 2012;19(9):1159-79.
64. Hansson O. Biomarkers for neurodegenerative diseases. Nat Med. 2021;27(6):954-63.
65. Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 2016;15(7):673-84.
66. Teunissen CE, Verberk IMW, Thijssen EH, Vermunt L, Hansson O, Zetterberg H, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. Lancet Neurol. 2022;21(1):66-77.
67. Wright BL, Lai JT, Sinclair AJ. Cerebrospinal fluid and lumbar puncture: a practical review. J Neurol. 2012;259(8):1530-45.
68. Spector R, Robert Snodgrass S, Johanson CE. A balanced view of the cerebrospinal fluid composition and functions: Focus on adult humans. Exp Neurol. 2015;273:57-68.
69. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nature reviews Neurology. 2010;6(3):131-44.
70. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimer's Research & Therapy. 2019;11(1):34.
71. Lewczuk P, Lelental N, Spitzer P, Maler JM, Kornhuber J. Amyloid-β 42/40 cerebrospinal fluid concentration ratio in the diagnostics of Alzheimer's disease: validation of two novel assays. Journal of Alzheimer's disease : JAD. 2015;43(1):183-91.
72. Alonso AD, Grundke-Iqbal I, Barra HS, Iqbal K. Abnormal phosphorylation of tau and the mechanism of Alzheimer neurofibrillary degeneration: sequestration of microtubule-associated proteins 1 and 2 and the

disassembly of microtubules by the abnormal tau. Proc Natl Acad Sci U S A. 1997;94(1):298-303.
73. de Jong D, Jansen RW, Kremer BP, Verbeek MM. Cerebrospinal fluid amyloid beta42/phosphorylated tau ratio discriminates between Alzheimer's disease and vascular dementia. J Gerontol A Biol Sci Med Sci. 2006;61(7):755-8.
74. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. Journal of Internal Medicine. 2018;284(6):643-63.
75. Jack CR, Jr., Wiste HJ, Weigand SD, Knopman DS, Mielke MM, Vemuri P, et al. Different definitions of neurodegeneration produce similar amyloid/neurodegeneration biomarker group findings. Brain. 2015;138(Pt 12):3747-59.
76. Debette S, Schilling S, Duperron MG, Larsson SC, Markus HS. Clinical Significance of Magnetic Resonance Imaging Markers of Vascular Brain Injury: A Systematic Review and Meta-analysis. JAMA Neurol. 2019;76(1):81-94.
77. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31(3):968-80.
78. Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex. 2009;19(3):497-510.
79. Yilmaz P, Ikram MK, Niessen WJ, Ikram MA, Vernooij MW. Practical Small Vessel Disease Score Relates to Stroke, Dementia, and Death. Stroke. 2018;49(12):2857-65.
80. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011;42(9):2672-713.
81. Moroni F, Ammirati E, Rocca MA, Filippi M, Magnoni M, Camici PG. Cardiovascular disease and brain health: Focus on white matter hyperintensities. Int J Cardiol Heart Vasc. 2018;19:63-9.
82. Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. Nature reviews Neurology. 2015;11(3):157-65.
83. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12(8):822-38.
84. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics. 2007;4(3):316-29.

85. Power MC, Su D, Wu A, Reid RI, Jack CR, Knopman DS, et al. Association of white matter microstructural integrity with cognition and dementia. Neurobiol Aging. 2019;83:63-72.
86. Martinez-Ramirez S, Greenberg SM, Viswanathan A. Cerebral microbleeds: overview and implications in cognitive impairment. Alzheimers Res Ther. 2014;6(3):33.
87. Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, et al. Perivascular spaces in the brain: anatomy, physiology and pathology. Nature reviews Neurology. 2020;16(3):137-53.
88. Shea YF, Chu LW, Chan AO, Ha J, Li Y, Song YQ. A systematic review of familial Alzheimer's disease: Differences in presentation of clinical features among three mutated genes and potential ethnic differences. J Formos Med Assoc. 2016;115(2):67-75.
89. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet. 2019;51(3):414-30.
90. Escott-Price V, Myers A, Huentelman M, Shoai M, Hardy J. Polygenic Risk Score Analysis of Alzheimer's Disease in Cases without APOE4 or APOE2 Alleles. The journal of prevention of Alzheimer's disease. 2019;6(1):16-9.
91. van der Lee SJ, Wolters FJ, Ikram MK, Hofman A, Ikram MA, Amin N, et al. The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study. Lancet Neurol. 2018;17(5):434-44.
92. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol. 2021;20(1):68-80.
93. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. Pathology. 2019;51(2):165-76.
94. Huang Y, Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. Neurobiol Dis. 2014;72 Pt A:3-12.
95. Norwitz NG, Saif N, Ariza IE, Isaacson RS. Precision Nutrition for Alzheimer's Prevention in ApoE4 Carriers. Nutrients. 2021;13(4).
96. Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med. 2008;12(6b):2762-71.
97. Bellenguez C, Küçükali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet. 2022;54(4):412-36.
98. Chasioti D, Yan J, Nho K, Saykin AJ. Progress in Polygenic Composite Scores in Alzheimer's and Other Complex Diseases. Trends Genet. 2019;35(5):371-82.

99. Najar J, van der Lee SJ, Joas E, Wetterberg H, Hardy J, Guerreiro R, et al. Polygenic risk scores for Alzheimer's disease are related to dementia risk in APOE ε4 negatives. Alzheimers Dement (Amst). 2021;13(1):e12142.
100. de Bruijn RF, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. BMC Med. 2014;12:130.
101. Walker KA, Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, et al. Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia. Jama. 2019;322(6):535-45.
102. Albanese E, Launer LJ, Egger M, Prince MJ, Giannakopoulos P, Wolters FJ, et al. Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. Alzheimers Dement (Amst). 2017;8:165-78.
103. Gustafson D. Adiposity indices and dementia. Lancet Neurol. 2006;5(8):713-20.
104. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. Lancet (London, England). 1996;347(9009):1141-5.
105. Gustafson DR, Bäckman K, Waern M, Ostling S, Guo X, Zandi P, et al. Adiposity indicators and dementia over 32 years in Sweden. Neurology. 2009;73(19):1559-66.
106. Luchsinger JA, Patel B, Tang MX, Schupf N, Mayeux R. Measures of adiposity and dementia risk in elderly persons. Arch Neurol. 2007;64(3):392-8.
107. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012;11(11):1006-12.
108. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nature reviews Neurology. 2018;14(11):653-66.
109. Najar J, Östling S, Gudmundsson P, Sundh V, Johansson L, Kern S, et al. Cognitive and physical activity and dementia: A 44-year longitudinal population study of women. Neurology. 2019;92(12):e1322-e30.
110. Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, et al. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2015;22:39-57.
111. Cao Q, Tan CC, Xu W, Hu H, Cao XP, Dong Q, et al. The Prevalence of Dementia: A Systematic Review and Meta-Analysis. Journal of Alzheimer's disease : JAD. 2020;73(3):1157-66.
112. Choi D, Choi S, Park SM. Effect of smoking cessation on the risk of dementia: a longitudinal study. Ann Clin Transl Neurol. 2018;5(10):1192-9.
113. Piazza-Gardner AK, Gaffud TJ, Barry AE. The impact of alcohol on Alzheimer's disease: a systematic review. Aging & mental health. 2013;17(2):133-46.
114. Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. Lancet Neurol. 2018;17(11):1006-15.

115. Riederer P, Korczyn AD, Ali SS, Bajenaru O, Choi MS, Chopp M, et al. The diabetic brain and cognition. J Neural Transm (Vienna). 2017;124(11):1431-54.
116. Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimers Dement (Amst). 2017;7:69-87.
117. Nooyens ACJ, Yildiz B, Hendriks LG, Bas S, van Boxtel MPJ, Picavet HSJ, et al. Adherence to dietary guidelines and cognitive decline from middle age: the Doetinchem Cohort Study. Am J Clin Nutr. 2021;114(3):871-81.
118. Solfrizzi V, Custodero C, Lozupone M, Imbimbo BP, Valiani V, Agosti P, et al. Relationships of Dietary Patterns, Foods, and Micro- and Macronutrients with Alzheimer's Disease and Late-Life Cognitive Disorders: A Systematic Review. Journal of Alzheimer's Disease. 2017;59(3):815-49.
119. Román GC, Jackson RE, Gadhia R, Román AN, Reis J. Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. Rev Neurol (Paris). 2019;175(10):724-41.
120. Tang PC, Ng YF, Ho S, Gyda M, Chan SW. Resveratrol and cardiovascular health--promising therapeutic or hopeless illusion? Pharmacol Res. 2014;90:88-115.
121. Morris MC. Nutrition and risk of dementia: overview and methodological issues. Annals of the New York Academy of Sciences. 2016;1367(1):31-7.
122. Shakersain B, Santoni G, Larsson SC, Faxén-Irving G, Fastbom J, Fratiglioni L, et al. Prudent diet may attenuate the adverse effects of Western diet on cognitive decline. Alzheimer's & Dementia. 2016;12(2):100-9.
123. Samadi M, Moradi S, Moradinazar M, Mostafai R, Pasdar Y. Dietary pattern in relation to the risk of Alzheimer's disease: a systematic review. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2019;40(10):2031-43.
124. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr. 1995;61(6 Suppl):1402s-6s.
125. Männikkö R, Komulainen P, Schwab U, Heikkilä HM, Savonen K, Hassinen M, et al. The Nordic diet and cognition--The DR's EXTRA Study. Br J Nutr. 2015;114(2):231-9.
126. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2015;11(9):1007-14.
127. Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M. Midlife healthy-diet index and late-life dementia and Alzheimer's disease. Dement Geriatr Cogn Dis Extra. 2011;1(1):103-12.

128. Krznarić Ž, Karas I, Ljubas Kelečić D, Vranešić Bender D. The Mediterranean and Nordic Diet: A Review of Differences and Similarities of Two Sustainable, Health-Promoting Dietary Patterns. Front Nutr. 2021;8:683678.
129. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol. 2006;59(6):912-21.
130. Shakersain B, Rizzuto D, Larsson SC, Faxén-Irving G, Fratiglioni L, Xu W-L. The Nordic Prudent Diet Reduces Risk of Cognitive Decline in the Swedish Older Adults: A Population-Based Cohort Study. Nutrients. 2018;10(2):229.
131. Petersson SD, Philippou E. Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence. Advances in nutrition (Bethesda, Md). 2016;7(5):889-904.
132. Liu YH, Gao X, Na M, Kris-Etherton PM, Mitchell DC, Jensen GL. Dietary Pattern, Diet Quality, and Dementia: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. Journal of Alzheimer's disease : JAD. 2020;78(1):151-68.
133. Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. Journal of Alzheimer's disease : JAD. 2014;39(2):271-82.
134. Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007;69(20):1921-30.
135. Hu EA, Wu A, Dearborn JL, Gottesman RF, Sharrett AR, Steffen LM, et al. Adherence to Dietary Patterns and Risk of Incident Dementia: Findings from the Atherosclerosis Risk in Communities Study. Journal of Alzheimer's disease : JAD. 2020;78(2):827-35.
136. Hsu TM, Kanoski SE. Blood-brain barrier disruption: mechanistic links between Western diet consumption and dementia. Frontiers in aging neuroscience. 2014;6:88.
137. Spector R. Nutrient transport systems in brain: 40 years of progress. J Neurochem. 2009;111(2):315-20.
138. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388-405.
139. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14(10):576-90.
140. Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 2021;320(3):C375-c91.
141. Oikonomou EK, Antoniades C. The role of adipose tissue in cardiovascular health and disease. Nat Rev Cardiol. 2019;16(2):83-99.

142. Marx W, Veronese N, Kelly JT, Smith L, Hockey M, Collins S, et al. The Dietary Inflammatory Index and Human Health: An Umbrella Review of Meta-Analyses of Observational Studies. Advances in nutrition (Bethesda, Md). 2021;12(5):1681-90.
143. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014;17(8):1689-96.
144. Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, et al. IL-1β, IL-6, TNF- α and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. Sci Rep. 2018;8(1):12050.
145. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, et al. Inflammation and Alzheimer's disease. Neurobiol Aging. 2000;21(3):383-421.
146. Gu Y, Vorburger R, Scarmeas N, Luchsinger JA, Manly JJ, Schupf N, et al. Circulating inflammatory biomarkers in relation to brain structural measurements in a non-demented elderly population. Brain Behav Immun. 2017;65:150-60.
147. McGrattan AM, McGuinness B, McKinley MC, Kee F, Passmore P, Woodside JV, et al. Diet and Inflammation in Cognitive Ageing and Alzheimer's Disease. Curr Nutr Rep. 2019;8(2):53-65.
148. Ozawa M, Shipley M, Kivimaki M, Singh-Manoux A, Brunner EJ. Dietary pattern, inflammation and cognitive decline: The Whitehall II prospective cohort study. Clin Nutr. 2017;36(2):506-12.
149. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, et al. Advanced Glycation End Products in Foods and a Practical Guide to Their Reduction in the Diet. Journal of the American Dietetic Association. 2010;110(6):911-6.e12.
150. Sato N, Morishita R. The roles of lipid and glucose metabolism in modulation of beta-amyloid, tau, and neurodegeneration in the pathogenesis of Alzheimer disease. Frontiers in aging neuroscience. 2015;7:199.
151. Sonestedt E, Hellstrand S, Drake I, Schulz CA, Ericson U, Hlebowicz J, et al. Diet Quality and Change in Blood Lipids during 16 Years of Follow-up and Their Interaction with Genetic Risk for Dyslipidemia. Nutrients. 2016;8(5).
152. Hill E, Goodwill MA, Gorelik A, Szoeke C. Diet and biomarkers of Alzheimer's disease: a systematic review and meta-analysis. Neurobiology of Aging. 2019;76:45-52.
153. Berti V, Walters M, Sterling J, Quinn CG, Logue M, Andrews R, et al. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. Neurology. 2018;90(20):e1789-e98.
154. Matthews DC, Davies M, Murray J, Williams S, Tsui WH, Li Y, et al. Physical Activity, Mediterranean Diet and Biomarkers-Assessed Risk of Alzheimer's: A Multi-Modality Brain Imaging Study. Adv J Mol Imaging. 2014;4(4):43-57.
155. Rainey-Smith SR, Gu Y, Gardener SL, Doecke JD, Villemagne VL, Brown BM, et al. Mediterranean diet adherence and rate of cerebral Aβ-

amyloid accumulation: Data from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing. Translational Psychiatry. 2018;8(1):238.
156. Vassilaki M, Aakre JA, Syrjanen JA, Mielke MM, Geda YE, Kremers WK, et al. Mediterranean Diet, Its Components, and Amyloid Imaging Biomarkers. J Alzheimers Dis. 2018;64(1):281-90.
157. Berti V, Murray J, Davies M, Spector N, Tsui WH, Li Y, et al. Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. Journal of Nutrition, Health and Aging. 2015;19(4):413-23.
158. Mosconi L, Murray J, Davies M, Williams S, Pirraglia E, Spector N, et al. Nutrient intake and brain biomarkers of Alzheimer's disease in at-risk cognitively normal individuals: a cross-sectional neuroimaging pilot study. BMJ open. 2014;4(6):e004850.
159. Merrill DA, Siddarth P, Raji CA, Emerson ND, Rueda F, Ercoli LM, et al. Modifiable Risk Factors and Brain Positron Emission Tomography Measures of Amyloid and Tau in Nondemented Adults with Memory Complaints. Am J Geriatr Psychiatry. 2016;24(9):729-37.
160. Hill E, Clifton P, Goodwill AM, Dennerstein L, Campbell S, Szoeke C. Dietary patterns and beta-amyloid deposition in aging Australian women. Alzheimer's & dementia (New York, N Y). 2018;4:535-41.
161. Hill E, Szoeke C, Dennerstein L, Campbell S, Clifton P. Adherence to the Mediterranean Diet Is not Related to Beta-Amyloid Deposition: Data from the Women's Healthy Ageing Project. The journal of prevention of Alzheimer's disease. 2018;5(2):137-41.
162. Drouka A, Mamalaki E, Karavasilis E, Scarmeas N, Yannakoulia M. Dietary and Nutrient Patterns and Brain MRI Biomarkers in Dementia-Free Adults. Nutrients. 2022;14(11).
163. Townsend RF, Woodside JV, Prinelli F, O'Neill RF, McEvoy CT. Associations Between Dietary Patterns and Neuroimaging Markers: A Systematic Review. Front Nutr. 2022;9:806006.
164. Akbaraly T, Sexton C, Zsoldos E, Mahmood A, Filippini N, Kerleau C, et al. Association of Long-Term Diet Quality with Hippocampal Volume: Longitudinal Cohort Study. Am J Med. 2018;131(11):1372-81.e4.
165. Jacka FN, Cherbuin N, Anstey KJ, Sachdev P, Butterworth P. Western diet is associated with a smaller hippocampus: a longitudinal investigation. BMC Med. 2015;13:215.
166. Corley J, Cox SR, Taylor AM, Hernandez MV, Maniega SM, Ballerini L, et al. Dietary patterns, cognitive function, and structural neuroimaging measures of brain aging. Exp Gerontol. 2020;142:111117.
167. Yassine HN, Finch CE. APOE Alleles and Diet in Brain Aging and Alzheimer's Disease. Frontiers in aging neuroscience. 2020;12:150.
168. Gentreau M, Chuy V, Féart C, Samieri C, Ritchie K, Raymond M, et al. Refined carbohydrate-rich diet is associated with long-term risk of dementia and Alzheimer's disease in apolipoprotein E ε4 allele carriers. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2020;16(7):1043-53.

169. Rydberg Sterner T, Ahlner F, Blennow K, Dahlin-Ivanoff S, Falk H, Havstam Johansson L, et al. The Gothenburg H70 Birth cohort study 2014-16: design, methods and study population. European journal of epidemiology. 2019;34(2):191-209.
170. Bengtsson C, Blohmé G, Hallberg L, Hällström T, Isaksson B, Korsan-Bengtsen K, et al. The study of women in Gothenburg 1968-1969--a population study. General design, purpose and sampling results. Acta Med Scand. 1973;193(4):311-8.
171. Rinder L, Roupe S, Steen B, Svanborg A. Seventy-year-old people in Gothenburg. A population study in an industrialized Swedish city. Acta Med Scand. 1975;198(5):397-407.
172. Rothenberg E, Bosaeus I, Steen B. Food habits and nutrient intake in three 70-year-old free-living populations in Gothenburg, Sweden. A 22-year cohort study1996. 104-10 p.
173. Eriksson BG, Mellström D, Svanborg A. Medical-social intervention in a 70-year-old Swedish population. A general presentation of methodological experience. Compr Gerontol C. 1987;1:49-56.
174. Bengtsson C, Ahlqwist M, Andersson K, Björkelund C, Lissner L, Söderström M. The Prospective Population Study of Women in Gothenburg, Sweden, 1968-69 to 1992-93. A 24-year follow-up study with special reference to participation, representativeness, and mortality. Scand J Prim Health Care. 1997;15(4):214-9.
175. Lissner L, Skoog I, Andersson K, Beckman N, Sundh V, Waern M, et al. Participation bias in longitudinal studies: experience from the Population Study of Women in Gothenburg, Sweden. Scand J Prim Health Care. 2003;21(4):242-7.
176. Samuelsson J, Rothenberg E, Lissner L, Eiben G, Zettergren A, Skoog I. Time trends in nutrient intake and dietary patterns among five birth cohorts of 70-year-olds examined 1971–2016: results from the Gothenburg H70 birth cohort studies, Sweden. Nutrition Journal. 2019;18(1):66.
177. Kern S, Zetterberg H, Kern J, Zettergren A, Waern M, Hoglund K, et al. Prevalence of preclinical Alzheimer disease: Comparison of current classification systems. Neurology. 2018;90(19):e1682-e91.
178. Fässberg MM, Vanaelst B, Jonson M, Sterner TR, Ahlner F, Wetterberg H, et al. Epidemiology of suicidal feelings in an ageing Swedish population: from old to very old age in the Gothenburg H70 Birth Cohort Studies. Epidemiol Psychiatr Sci. 2019;29:e26.
179. Rothenberg E, Bosaeus I, Lernfelt B, Landahl S, Steen B. Rothenberg E, Bosaeus I, Lernfelt B, Landahl S, Steen B. Energy intake and expenditure: validation of a diet history by heart rate monitoring, activity diary and doubly labeled water. Eur J Clin Nutr 52, 832-8381998. 832-8 p.
180. Ax E, Warensjö Lemming E, Becker W, Andersson A, Lindroos AK, Cederholm T, et al. Dietary patterns in Swedish adults; results from a national dietary survey. Br J Nutr. 2016;115(1):95-104.

181. Vermeulen E, Stronks K, Visser M, Brouwer IA, Snijder MB, Mocking RJT, et al. Dietary pattern derived by reduced rank regression and depressive symptoms in a multi-ethnic population: the HELIUS study. Eur J Clin Nutr. 2017;71(8):987-94.
182. Shin D, Lee KW, Kim MH, Kim HJ, An YS, Chung HK. Identifying Dietary Patterns Associated with Mild Cognitive Impairment in Older Korean Adults Using Reduced Rank Regression. Int J Environ Res Public Health. 2018;15(1).
183. Biesbroek S, van der AD, Brosens MC, Beulens JW, Verschuren WM, van der Schouw YT, et al. Identifying cardiovascular risk factor-related dietary patterns with reduced rank regression and random forest in the EPIC-NL cohort. Am J Clin Nutr. 2015;102(1):146-54.
184. Batis C, Mendez MA, Gordon-Larsen P, Sotres-Alvarez D, Adair L, Popkin B. Using both principal component analysis and reduced rank regression to study dietary patterns and diabetes in Chinese adults. Public Health Nutr. 2016;19(2):195-203.
185. Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. Eur J Clin Nutr. 1991;45(12):569-81.
186. Rothenbreg E, Bosaeus I, Steen B. Evaluation of energy intake estimated by a diet history in three free-living 70 year old populations in Gothenburg, Sweden. Eur J Clin Nutr. 1997;51(1):60-6.
187. Samuelsson J, Kern S, Zetterberg H, Blennow K, Rothenberg E, Wallengren O, et al. A Western-style dietary pattern is associated with cerebrospinal fluid biomarker levels for preclinical Alzheimer's disease-A population-based cross-sectional study among 70-year-olds. Alzheimer's & dementia (New York, N Y). 2021;7(1):e12183.
188. Samuelsson J, Najar J, Wallengren O, Kern S, Wetterberg H, Mellqvist Fässberg M, et al. Interactions between dietary patterns and genetic factors in relation to incident dementia among 70-year-olds. Eur J Nutr. 2021.
189. Jack CR, Jr., Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology. 2016;87(5):539-47.
190. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol. 2006;5(3):228-34.
191. Vanmechelen E, Vanderstichele H, Davidsson P, Van Kerschaver E, Van Der Perre B, Sjögren M, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. Neurosci Lett. 2000;285(1):49-52.
192. Zetterberg H, Wahlund LO, Blennow K. Cerebrospinal fluid markers for prediction of Alzheimer's disease. Neurosci Lett. 2003;352(1):67-9.

193. Asberg M, Montgomery SA, Perris C, Schalling D, Sedvall G. A comprehensive psychopathological rating scale. Acta Psychiatr Scand Suppl. 1978(271):5-27.
194. Gottfries CG, Bråne G, Gullberg B, Steen G. A new rating scale for dementia syndromes. Arch Gerontol Geriatr. 1982;1(4):311-30.
195. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry. 1982;140:566-72.
196. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.
197. Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A. A population-based study of dementia in 85-year-olds. N Engl J Med. 1993;328(3):153-8.
198. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984;141(11):1356-64.
199. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders (DSM-III-R). 1987.
200. Saltin B, Grimby G. Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. Circulation. 1968;38(6):1104-15.
201. Rodjer L, Jonsdottir IH, Rosengren A, Bjorck L, Grimby G, Thelle DS, et al. Self-reported leisure time physical activity: a useful assessment tool in everyday health care. BMC public health. 2012;12:693.
202. Statistics Sweden. Svensk utbildningsklassifikation (SUN) 2000. https://www.scb.se/contentassets/aeeedec0e28c465aa524429407dcd5ba/mis-sun-2000.pdf.
203. Hörnell A, Berg C, Forsum E, Larsson C, Sonestedt E, Åkesson A, et al. Perspective: An Extension of the STROBE Statement for Observational Studies in Nutritional Epidemiology (STROBE-nut): Explanation and Elaboration. Advances in nutrition (Bethesda, Md). 2017;8(5):652-78.
204. Cade JE, Burley VJ, Warm DL, Thompson RL, Margetts BM. Food-frequency questionnaires: a review of their design, validation and utilisation. Nutr Res Rev. 2004;17(1):5-22.
205. Lemming EW, Pitsi T. The Nordic Nutrition Recommendations 2022 - food consumption and nutrient intake in the adult population of the Nordic and Baltic countries. Food Nutr Res. 2022;66.
206. Burke BS. The Dietary History as a Tool in Research1. Journal of the American Dietetic Association. 1947;23(12):1041-2.
207. Mattisson I, Wirfält E, Aronsson CA, Wallström P, Sonestedt E, Gullberg B, et al. Misreporting of energy: prevalence, characteristics of misreporters and influence on observed risk estimates in the Malmö Diet and Cancer cohort. Br J Nutr. 2005;94(5):832-42.
208. Black AE, Cole TJ. Biased over- or under-reporting is characteristic of individuals whether over time or by different assessment methods. J Am Diet Assoc. 2001;101(1):70-80.

209. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13(1):3-9.
210. Hoffmann K, Schulze MB, Schienkiewitz A, Nöthlings U, Boeing H. Application of a new statistical method to derive dietary patterns in nutritional epidemiology. Am J Epidemiol. 2004;159(10):935-44.
211. Zhao J, Li Z, Gao Q, Zhao H, Chen S, Huang L, et al. A review of statistical methods for dietary pattern analysis. Nutr J. 2021;20(1):37.
212. Wancata J, Börjesson-Hanson A, Ostling S, Sjögren K, Skoog I. Diagnostic criteria influence dementia prevalence. Am J Geriatr Psychiatry. 2007;15(12):1034-45.
213. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011;11:450.
214. Rizzuto D, Feldman AL, Karlsson IK, Dahl Aslan AK, Gatz M, Pedersen NL. Detection of Dementia Cases in Two Swedish Health Registers: A Validation Study. Journal of Alzheimer's disease : JAD. 2018;61(4):1301-10.
215. Durand CP. Does raising type 1 error rate improve power to detect interactions in linear regression models? A simulation study. PLoS One. 2013;8(8):e71079.
216. Hossain S, Beydoun MA, Kuczmarski MF, Tajuddin S, Evans MK, Zonderman AB. The Interplay of Diet Quality and Alzheimer's Disease Genetic Risk Score in Relation to Cognitive Performance Among Urban African Americans. Nutrients. 2019;11(9).
217. Barberger-Gateau P, Samieri C, Féart C, Plourde M. Dietary omega 3 polyunsaturated fatty acids and Alzheimer's disease: interaction with apolipoprotein E genotype. Curr Alzheimer Res. 2011;8(5):479-91.
218. Samieri C, Lorrain S, Buaud B, Vaysse C, Berr C, Peuchant E, et al. Relationship between diet and plasma long-chain n-3 PUFAs in older people: impact of apolipoprotein E genotype. J Lipid Res. 2013;54(9):2559-67.
219. Rydén L, Sacuiu S, Wetterberg H, Najar J, Guo X, Kern S, et al. Atrial Fibrillation, Stroke, and Silent Cerebrovascular Disease: A Population-based MRI Study. Neurology. 2021;97(16):e1608-e19.
220. Winter JE, MacInnis RJ, Wattanapenpaiboon N, Nowson CA. BMI and all-cause mortality in older adults: a meta-analysis. Am J Clin Nutr. 2014;99(4):875-90.
221. Swedish Board of Agriculture. Livsmedelskonsumtionen i siffror - Hur har konsumtionen utvecklats de senaste femtio åren och varför. https://webbutiken.jordbruksverket.se/sv/artiklar/ra1515.html; 2015.
222. Martínez-Lapiscina EH, Galbete C, Corella D, Toledo E, Buil-Cosiales P, Salas-Salvado J, et al. Genotype patterns at CLU, CR1, PICALM and APOE, cognition and Mediterranean diet: the PREDIMED-NAVARRA trial. Genes Nutr. 2014;9(3):393.
223. Huang TL, Zandi PP, Tucker KL, Fitzpatrick AL, Kuller LH, Fried LP, et al. Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. Neurology. 2005;65(9):1409-14.

224. Samieri C, Morris MC, Bennett DA, Berr C, Amouyel P, Dartigues JF, et al. Fish Intake, Genetic Predisposition to Alzheimer Disease, and Decline in Global Cognition and Memory in 5 Cohorts of Older Persons. Am J Epidemiol. 2018;187(5):933-40.
225. Vu THT, Beck T, Bennett DA, Schneider JA, Hayden KM, Shadyab AH, et al. Adherence to MIND Diet, Genetic Susceptibility, and Incident Dementia in Three US Cohorts. Nutrients. 2022;14(13).
226. Topiwala A, Allan CL, Valkanova V, Zsoldos E, Filippini N, Sexton C, et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. Bmj. 2017;357:j2353.