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Diet and common neurological disorders: cohort studies on dementia, Parkinson's disease, and stroke

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Abstract

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Risk factors for dementia, Parkinson's disease, and stroke have been widely studied but there are still research gaps concerning the role of diet for the development of these diseases. The overall aim of this thesis was to investigate whether various aspects of diet are associated with common disorders and diseases in the brain.

Paper I and II are based on the Uppsala Longitudinal Study of Adult Men (ULSAM). Paper III and IV are based on the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM).

In paper I, we investigated the associations between three different dietary patterns and incidence of Alzheimer's disease (AD), dementia, and cognitive impairment. We observed no associations between adherence to the Healthy Diet Indicator and any of the outcomes studied, or between adherence to a Mediterranean-like diet (mMDS) and AD or dementia. There was a tendency towards a lower risk of cognitive impairment with higher adherence to the mMDS, and a weak association between adherence to a Low Carbohydrate High Protein score and higher risk of all-type dementia. Overall, there were no strong associations with the studied dietary patterns and development of dementia or cognitive impairment.

In paper II, we found no associations of vitamin D measured as vitamin D intake, plasma 25-hydroxyvitamin D concentrations, or a vitamin D synthesis genetic risk score with incident AD, vascular dementia, dementia, or performance in the Mini-Mental State Examination.

In paper III, we observed a weak higher risk of PD associated with milk consumption but there was no dose-response relationship. Thus, this association needs to be interpreted with caution. Fermented milk intake was not associated with PD.

In paper IV, we found that a higher long-term milk consumption based on repeated measures of intake was not associated with total stroke, weakly and non-linearly associated with lower risk of cerebral infarction and higher risk of hemorrhagic stroke. Fermented milk consumption was not associated with any stroke type. Our results highlight the importance of repeated measurements of food intake, separate analyses of milk and fermented milk consumption, and to study stroke types separately.

Despite the lack of strong associations, the findings of this thesis have increased our knowledge about the potential role of overall diet, vitamin D, and milk and fermented consumption in the prevention or development of common neurodegenerative diseases and stroke.

Keywords: diet, dietary pattern, Healthy Diet Indicator, Mediterranean diet, low carbohydrate, vitamin D, 25-hydroxyvitamin D, Mendelian randomization, milk, fermented milk, epidemiology, cohort study, Alzheimer's disease, dementia, cognitive impairment, Parkinson's disease, stroke

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To my family

List of Papers

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

I Olsson, E., Karlström, B., Kilander, L., Byberg, L., Cederholm, T., and Sjögren, P. (2015) Dietary Patterns and Cognitive Dysfunction in a 12-Year Follow-up Study of 70 Year Old Men. *Journal of Alzheimer's Disease,* 43(1):109–119.

II Olsson, E., Byberg, L., Karlström, B., Cederholm, T., Melhus, H., Sjögren, P., and Kilander, L. (2017) Vitamin D Is Not Associated with Incident Dementia or Cognitive Impairment: An 18-y Follow-up Study in Community-living Old Men. *American Journal of Clinical Nutrition*, 105(4):936-943.

III Olsson, E., Byberg, L., Höijer, J., Kilander, L., and Larsson, S.C. (2020) Milk and Fermented Milk Intake and Parkinson's Disease: Cohort Study. *Nutrients,*12(9):2769.

IV Olsson, E., Larsson, S.C., Höijer, J., Kilander, L., and Byberg, L. (2021) Milk and Fermented Milk Consumption and Risk of Stroke: Longitudinal study. Manuscript.

Contents

Abbreviations

AD	Alzheimer's disease
APOE	Apolipoprotein E gene
BMI	Body mass index
CI	Confidence interval
COSM	Cohort of Swedish Men
DAG	Directed acyclic graph
DBP	Vitamin D binding protein
EE	Energy expenditure
EI	Energy intake
E%	Percentage of energy
FFQ	Food Frequency Questionnaires
GRS	Genetic risk score
HDI	Healthy Diet Indicator
HR	Hazard ratio
LCHP	Low-Carbohydrate High-Protein Score
mMDS	Modified Mediterranean Diet Score
MMSE	Mini Mental State Examination
MR	Mendelian randomization
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association
NPR	National Patient Register
OR	Odds ratio
ORFR	Optically readable food record
PAL	Physical activity level
PD	Parkinson's disease
P	Points
PUFA	Polyunsaturated fatty acids
SD	Standard deviation
SFA	Saturated fatty acids
SMC	Swedish Mammography Cohort
SNP	Single nucleotide polymorphism
ULSAM	Uppsala Longitudinal Study of Adult Men
VAD	Vascular dementia

WHO	World Health Organization
WT	Weighted record
25(OH)D	25-hydroxyvitamin D

Introduction

Dementia, Parkinson's disease (PD) and stroke are common disorders in the brain and affect many people. Both Alzheimer's disease (AD), the most common cause of dementia, and PD are neurodegenerative diseases where the progression of the disease varies and usually develops slowly over many years. Symptoms of stroke, on the other hand, appear suddenly without warning and can change the life of a person who has been healthy and independent to become completely dependent on the help of others. These diseases cause a wide range of complications, such as functional impairments, and tremendous suffering for the affected person, their families and others in their vicinity. Also, health care costs are high for these diseases. Although risk factors for dementia, PD, and stroke have been widely studied there are still research gaps concerning the role of diet in the development of these diseases. Today there are symptom relieving medications but still no cure for either AD or PD. Therefore, identification of modifiable factors, such as diet, that have the potential to affect the risk of these diseases is of great importance. In this thesis I investigated whether different aspects of diet influence these common brain disorders. Specifically, we studied whether different diets and vitamin D may play a role in the prevention of dementia and cognitive decline and whether consumption of milk and fermented milk affects the risk of developing PD and stroke in Swedish middle-aged and older women and men.

Background

Dementia

Dementia is an umbrella term (a syndrome) for cognitive decline caused by changes in the brain that are not part of the normal aging progress and affects daily activities. It is defined as impairment of memory and at least one other cognitive function, lasting for more than six months and affecting the ability to manage activities in daily life. The symptoms can vary with stages of dementia and can include memory loss, problems with thinking, reasoning, orientation, judgment, and problem solving. Mood, emotions, and behavior can also be affected. The World Health Organization (WHO) estimated that 55.2 million people were living with dementia worldwide in 2019 (1). In Sweden around 20,000 to 25,000 people are identified with dementia every year and today 130-150,000 persons are living with dementia (2, 3). The number of people with dementia will increase and according to the World Alzheimer report 2018 around 152 million people will be living with dementia by 2050 (4).

Alzheimer's disease (AD) is the most common form of dementia and accounts for 60% of all dementia cases. The pathological changes leading up to the disease can start 15-20 years before any signs of symptoms (5, 6). The neurodegeneration usually starts in the hippocampal area, affecting episodic memory, i.e., memory for recent events (7). Gradually, verbal, visuospatial and perceptual functions are affected, as well as impairment of problem solving and logical thinking. Executive dysfunction, such as lack of drive, is common. Other later symptoms are difficulties with speaking, walking, standing, and swallowing. At the end stage the person will be bedbound and need help with everything from dressing to eating (8). The pathology of AD is characterized by aggregation of the protein beta-amyloid in plaques outside the neurons, and tangles of tau deposition inside the neurons. The plaques enhance neurodegeneration, and the tangles prevent transportation of nutrients in the neurons. The start of the neurodegeneration is not yet fully understood but one theory is that aggregation of amyloid beta, starts the process and promotes hyper-phosphorylation of the tau protein into neurofibrillary tangles (9, 10). This causes synaptic dysfunction (where the synapses are blocked and thus the neurons cannot communicate) and leads to neuronal death (8, 11). Other characteristics are inflammation, microglial activation, and neurodegeneration (8). The diagnosis of AD includes a medical examination, cognitive tests as well as blood tests and brain imaging. Biomarkers in cerebrospinal fluid may

aid in diagnostics. Decreased concentrations of amyloid beta, and increased concentrations of total tau and phosphorylated tau are typical findings in AD (8).

Vascular dementia is the second most common form of dementia and is caused by shortage of blood supply to the brain due to ischemic or hemorrhagic strokes and/or small vessel brain disease (12). Early symptoms are problems with executive functions like difficulties with initiation, planning, and implementation, but usually not loss of memory as in Alzheimer's disease. Known risk factors are hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking and overweight, the same risk factors as for cardiovascular disease.

Frontotemporal dementia (13), Lewy Body dementia (14), and Parkinson's disease with dementia (14) are other forms of dementia. The term unspecified dementia is used when it is not possible to establish type of dementia or there are multiple pathologies (15).

It is important to have valid methods to measure cognitive decline and cognitive impairment for early detection and diagnosis of dementia, distinguishing between normal cognitive decline due to age or if it is due to dementia, defining areas that are affected, and thus adapt the care to the individual (16). There are many instruments for measuring cognitive decline. The Mini Mental State Examination (MMSE) (17) is the most common screening test of cognitive function and is widely used, both in clinical practice and in research. It includes brief questions on orientation to time and place, attention/calculation, short-term memory, praxis and figure copying, and the maximal score is 30 points. However, it is complicated to measure cognitive function even in normal aging due to variability among persons (18). The test results can be unspecific, may not mirror daily life functioning, and educational level may influence the test results to mask cognitive decline (18).

Today there are no medications that cure AD. It is discussed that any such future treatment would need to start very early in the neurodegeneration process to have an effect on the degeneration. High age, family history of having a first degree relative with AD, and heredity such as the apolipoprotein E e4 genotype are known non-modifiable risk factors for AD. Some cardiovascular risk factors such as hypertension, smoking, diabetes, hyperlipidemia, and obesity have been associated with increased risk of dementia including AD (19). Other potential risk factors include low education, hearing impairment, depression, physical inactivity, low social contact, alcohol consumption, traumatic brain injury, and air pollution (20).

Parkinson's disease

Parkinson's disease (PD) was first described in the literature by James Parkinson in 1817 (21). This disease is the second most common neurodegenerative

disease in the world. Approximately 6 million people suffer from PD worldwide (22) and in Sweden around 22,000 people are currently diagnosed with PD (23). PD is more common in higher ages and the prevalence is around 1% in the population above the age of 60 years and at the age of 80 years the prevalence is around 4% (24). The incidence rates vary among studies but rates of 3-258 per 100,000 person-years have been reported (25).

PD is characterized by loss of dopamine-producing brain cells in substantia nigra. Dopamine is a neurotransmitter involved in controlling movements of the body. The main symptoms in PD are bradykinesia (slowness or absence of voluntary movements), tremor, rigidity, and postural instability. Other common symptoms are constipation, anosmia, sleep disturbance, depression, and further on cognitive impairment (26). Lewy bodies with the aggregated form of alpha-synuclein have been found inside the remaining neurons in persons with PD and this aggregation is considered a hallmark of PD (27, 28). Today there is no cure for PD. Dopaminergic medications are designed to increase, substitute or prolong the effect of dopamine in the brain and alleviate symptoms (29). Deep brain stimulation improves mobility and reduces tremor in selected patients.

Risk factors for PD are high age and genetic factors. However, genetic factors are considered to account for only 5-10% of PD cases (30). Thus, environmental factors like exposure to toxins and pesticides or lifestyle factors such as diet may play an important role in the PD pathogenesis (31, 32). Smoking and coffee consumption have been associated with decreased risk of PD in observational studies (31). The cause of PD is not completely known but inflammation, oxidative stress, and disturbances in the gut microbiota are among the processes suggested to be involved in the pathogenesis (33-39).

Stroke

Worldwide, stroke is the second most common cause of death and disability (40) with over 13 million new stroke cases every year (40, 41). A stroke can be a life-threatening condition. A person with a stroke needs immediate medical care to save the life of the person and reduce the brain damage. Approximately one third die and one third have permanent disabilities. According to The National Board of Health and Welfare, there were 27,500 stroke cases in Sweden in 2019 and 74% of those who had a stroke were 70 years old or older (42). In 1980, the WHO defined stroke as “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin” (43). The two main types of stroke are cerebral infarction or ischemic stroke, and hemorrhagic stroke. A stroke occurs when the brain does not get enough supply of blood and thus not enough oxygen which causes neuronal death. Cerebral infarction is the most common form, and accounts for approximately 87%

of the strokes cases (44), and is caused by a blocked artery by a cardiac emboli (blood clot due to atrial fibrillation) or rupture of a atherosclerotic plaque (45). Hemorrhagic stroke is caused by a rupture of the artery (intracerebral hemorrhage) or an intracerebral bleeding or a bleeding in the subarachnoid space (45, 46). Intracerebral hemorrhage accounts for 10-20% of all stroke cases (41). Treatment of an acute stroke at the emergency ward depends on whether it is a cerebral infarction or a hemorrhagic stroke. In brief, treatment with a thrombolytic agent may completely or partially resolve the blood clot when given within 4.5 hours from the onset of symptoms. The blood clot can also be removed with a stent retrieve. This procedure must be done within 6-24 hours of the first symptoms. The acute treatment for hemorrhagic stroke is to stop the bleeding and control the pressure in the brain and may involve medication to lower pressure in the brain and/or surgery. The consequences of stroke depend on which area in the brain that is affected and how severe the damage is. Common short- and long-term consequences of a stroke are complete or partial unilateral paralysis of the limbs. Other functions than can be affected are speech, language and communication, swallowing (dysphagia), vision, balance, memory and cognitive functions (47).

Non-modifiable risk factors for stroke are high age, sex (more common in men), and ethnicity. Hypertension is a major risk factor for both cerebral infarction and hemorrhagic stroke. Other modifiable risk factors for cerebral infarction are physical inactivity, obesity (particularly abdominal obesity), current smoking, type 2 diabetes mellitus, hyperlipidemia, high alcohol consumption (particularly for hemorrhagic stroke), and cardiac disease (such as atrial fibrillation, coronary heart disease, and carotid artery disease). Results from the INTERSTROKE study, including 32 countries, also included apolipoprotein (Apo)B/ApoA1 ratio, diet (low adherence to healthy dietary pattern) and psychosocial factors as risk factors. Risk factors that have been identified with hemorrhagic stroke are hypertension as mentioned earlier, physical inactivity, unhealthy diet, abdominal obesity, psychosocial factors, cardiac causes, and high alcohol consumption (48). Furthermore, abnormally formed blood vessels increase the risk of hemorrhagic stroke.

Dietary factors

In my profession as a dietitian at the Geriatric and Metabolic clinics, I met patients with dementia, PD, and stroke who had a variety of nutritional problems. These problems could include chewing and swallowing problems (dysphagia), dehydration, loss of appetite, changes in smell and taste, difficulties in preparing meals, the patient would forget to eat and drink, constipation, and malnutrition. As a dietitian, I do not only identify and treat nutrition related diseases and problems and conduct nutritional therapy but also support people to change their dietary intake and dietary habits. The aim is to improve their

health and prevent diseases such as diabetes, cardiovascular disease, overweight and obesity, and certain forms of cancer. But is there any evidence for nutritional advice for preventing or delaying dementia, PD, and stroke? What can I recommend as a dietitian to prevent or delay these diseases? As mentioned earlier, advanced age, heredity and certain genes are risk factors for dementia, PD, and stroke but we cannot change these factors. Dietary intake on the other hand is a lifestyle factor that is modifiable. The diet may affect dementia, PD, and stroke through several mechanisms and pathways, including the diet's effect on oxidative stress, inflammation, gut microbiota, body weight, blood pressure, glucose, insulin, and blood lipids (20, 49, 50).

To study the impact of dietary intake is complex and challenging. We eat food in combination and the compounds (both known and unknown) in food are often inter correlated and have synergistic effects. We can study the impact of diet by focusing on single nutrients, foods, and dietary patterns. There are different methods for measuring dietary intake and the most common measurements in nutritional epidemiology are food frequency questionnaires (FFQ), 24-h recall interviews, and food records. In this thesis, dietary intake was measured with food records in Paper I and Paper II and with FFQ in Paper III and Paper IV.

In food records, foods and drinks are recorded at the time when it is consumed. The food recording can be very detailed and may include measuring the amount of food consumed, recording of time and type of meal, preparation, and brands among others. In food records the participants do not need to rely on memory but recording of the diet may influence the intake. Further, the number of days required to measure habitual intake to classify food and nutrient intake into categories and rank the participants' intake depends on the population and the research question but around 7-14 days have been suggested (51). The FFQ assesses the habitual intake usually covering the past 6-12 months and includes a list of foods and drinks with questions on how often the food was eaten. Pictures of portion sizes can also be included in the FFQ. The estimated usual dietary intakes can be ranked between participants after adjustment for total energy intake (52). The FFQ relies on the participant's memory to recall what was consumed and how often the food was consumed but is less demanding and less time consuming than food records.

In Paper I, focus was on dietary patterns and dementia. In dietary patterns we are able to study different dietary components in combination (53). We used a priori dietary patterns which are based on predefined indices and can include foods, nutrients, and quantities of macronutrients. These a priori dietary patterns are often based on recommendations for prevention of diseases and/or dietary habits proposed to be healthy (54). The Healthy Diet Indicator (HDI) is based on the WHO dietary guidelines for prevention of chronic diseases and is characterized by high intakes of fruit and vegetables (<400g/d), dietary fiber (27-40g/d), pulses, nuts, seeds (>30g/d), and complex carbohydrates (50-70 Energy (E)%), adequate intakes of protein (10-50 E%), and poly

unsaturated fatty (PUFA, 3-7 E%), limited amounts of saturated fatty acids (SFA, ≤10 E%), oligo-/mono- and disaccharides ≤10 E%, and cholesterol (≤300 mg/d) (55, 56). The Mediterranean Diet score was developed by Trichopoulou et al (57) and is based on the traditional dietary habits in the Mediterranean and is characterized by a high intakes of olive oil, fruit and vegetables, legumes, nuts, whole grain cereals, fish (moderate to high), and low intakes of saturated fats, meat and poultry, low to moderate intakes of dairy product (mainly yogurt and cheese), and a moderate intake of alcohol, preferably wine served with meals (57). The low carbohydrate high protein score is based on quantities of the macronutrients, carbohydrates and protein. A diet low in carbohydrates and high in protein has been suggested to be beneficial for weight loss management (58-60) and was promoted in the Swedish press and became popular in the general Swedish population in the beginning of 2000 (61). However, high adherence to LCHP has been associated with all-cause mortality (60, 62, 63). Type of carbohydrates or protein source is not taken into account in this dietary pattern and a high adherence to LCHP may lead to a high intake in total fat and saturated fats (60).

In Paper II, the focus was on vitamin D. The potential role of vitamin D in dementia was investigated in three different ways, including dietary vitamin D intake, plasma 25-hydroxyvitamin D (25(OH)D), a biomarker for vitamin D status, and a genetic risk score for vitamin D synthesis.

In Paper III and IV, we focused on the associations between milk products and risk of PD and stroke. Milk consumption is traditionally high in the Swedish population and milk products have been promoted as a nutritious drink. However, a high non-fermented milk consumption was associated with higher mortality and with markers of oxidative stress and inflammation among participants in the Swedish Cohort of Women (SMC) and the Cohort of Swedish Men (COSM) (64). On the other hand, high fermented milk consumption was associated with lower mortality and lower concentrations of markers of oxidative stress and inflammation (64). Inflammation and oxidative stress have been suggested to be involved in the pathogenesis of PD and stroke and this is one of the reasons why we were interested in investigating the link between milk and fermented milk intake and risk of PD and stroke.

Diet and dementia

Observational studies have investigated the impact of nutrients, foods, and healthy diets on AD and other dementia disorders. There is some evidence that a healthy dietary pattern, preferably plant-based diets and especially the Mediterranean diet, is associated with lower risk of cognitive decline and lower risk of AD and dementia, but the results are not consistent (20, 65-69). Concerning the Mediterranean diet, higher adherence to the Mediterranean diet was associated with reduced risk of AD in three longitudinal studies (70-72), while two other longitudinal studies did not observe an association between

high adherence to the Mediterranean diet and risk of AD or dementia (73, 74). At the time when we started our study, little data were available on the associations between traditional healthy diets based on the WHO recommendations and risk of dementia (56). Furthermore, observational data in Northern Europe investigating the impact of dietary patterns on dementia were limited to a small study in 425 Finnish participants that found that a healthy diet at midlife was associated with a decreased risk of AD and dementia (69).

The low carbohydrate and high protein diet (LCHP) has been promoted for short term weight loss but have also been associated with all-cause mortality (60). The impact of LCHP on the risk of AD and dementia had not been studied.

Since our publication on dietary patterns and dementia in 2015, several new studies on this topic have been published (75), including a couple of studies in the Northern part of Europe (76, 77).

Vitamin D

Vitamin D has been proposed to have an important role for brain health and the progression of cognitive impairment, AD, and dementia (78-84). Inflammation and oxidative stress may be involved in the pathogenesis of AD and dementia and vitamin D is suggested to be neuroprotective by reducing inflammation and oxidative stress (85-87). Vitamin D may also be involved in amyloid plaque clearance (88, 89). Vitamin D is obtained manly from sun exposure but diet is also an important source. There are two forms of vitamin D; vitamin D2 and vitamin D3. Mushrooms contain vitamin D2. Major dietary sources of vitamin D3 are fatty fish such as salmon, herring, and mackerel. Other dietary sources of vitamin D3 are egg, meat, and fortified dairy products, such as milk and margarines. In the skin, ultraviolet B sunlight transforms the cholesterol metabolite 7-dehydrocholesterol into pre-vitamin D3 (cholecalciferol). The enzyme 7-dehydrocholesterol reductase (DHCR7) is involved in this synthesis. The pre-vitamin is then converted into vitamin D3, also in the skin. Vitamin D3 is transported by vitamin D-binding protein (DBP) to the liver but can also be stored in the adipocytes. In the liver, vitamin D is converted into 25-hydroxyvitamin D. Vitamin D hydroxylase (CYP2R1) is involved in this process. 25(OH)D is then released into the bloodstream and plasma. 25(OH)D is considered the main clinical biomarker of vitamin D status but is still in its inactive form. In the kidneys, 25(OH)D is converted by hydroxylation to the biologically active form of vitamin D, that is 1,25-dihydroxyvitamin D, which is a steroid like hormone. This form of vitamin D is transported by DBP to the target cells were 1,25-dihydroxyvitamin D interacts with the vitamin D receptor. Vitamin D receptors have been found not only in vascular cells, muscle cells, and immune cells but also in brain cells and especially in areas where memory and cognitive functions are processed (87, 90-92).

Vitamin D and dementia

High intakes of vitamin D have been proposed to decrease the dementia risk, but the evidence is limited. In a cohort of 498 women followed for 7 years, a high vitamin D intake was found to be associated with lower risk of AD but not with non-AD dementias (93). A later study linked higher vitamin D intakes to decreased risk of dementia among 1759 multiethnic participants followed for 5.8 years (94).

Low concentrations of vitamin D have been associated with increased cognitive impairment, AD and dementia, especially in cross sectional studies and studies with short follow-up (95-97). In cross-sectional studies and studies with short follow-up there is a risk for reverse causation. Cognitive impairment and dementia may lead to poor nutritional intake and low sun exposure which may result in lower concentrations of vitamin D (98). In studies with longer follow-up, the evidence for an association between low vitamin D status is less convincing (99). Up until 2016, four out of six longitudinal studies observed no association between AD and dementia (79, 99-101), one study observed a higher risk of AD with low vitamin D status (82), and another observed a lower risk of dementia with higher concentrations of 25(OH)D (102). Later studies have also shown conflicting results (80, 83, 94, 103). The discrepancies among the studies could be due to different measurements methods of plasma 25(OH)D, different cut-offs for vitamin D deficiency, different tests for measurement of cognitive function, different follow-up times, and differences in ascertainment of diagnosis of dementia where some have used registers while others have followed up participants at the clinic. With the insidious onset of dementia, observations may be biased by reverse causation.

The Mendelian randomization approach (MR) can reduce confounding and reverse causation in observational studies by utilizing of genetic variants that are randomly assigned at conception. Only a few studies had examined the association of genetic variants involved in the vitamin D synthesis with cognitive impairment and AD before 2017 when we conducted our study. One previous MR study reported suggestive evidence between genetically predicted higher 25(OH)D concentrations and lower risk of AD (104). Another study reported no clear associations between genetic variants including *CYP2R1* and cognitive performance (105) but genetic variants associated with higher 25(OH)D and poorer word recall was observed in another study (106). Subsequent studies have reported that genetically predicted vitamin D concentration is inversely associated with AD (81, 107, 108).

In the Mendelian randomization approach, the genetic variants used as instrumental variables must be associated with the exposure and thus the causal relationship between the genetic variant(s) and the outcome can be studied. Genetic variants involved in the vitamin D synthesis have been associated with plasma 25(OH)D. The principles of the MR approach are illustrated in Figure 1. I will demonstrate the principles of MR by using our own study as

an example. A genetic risk score was created based on single nucleotide polymorphisms (SNPs) of the *DHCR7* and *CYP2R1* genes involved in the synthesis of vitamin D. The genetic risk score is associated with higher circulating levels of vitamin D and is then used as an unbiased proxy for plasma 25(OH)D. This genetic risk score is the instrument (G) in our instrumental variable analysis and influences the exposure X [plasma 25(OH)D], shown in Figure 1. The genetic risk score (G) is not associated with possible confounders (U) of the plasma 25(OH)D-outcome (Y) association. G may, further, not influence the outcome Y (AD, vascular dementia, dementia, cognitive impairment) in any other way except through exposure X [plasma 25(OH)D] (109, 110). It is important that the genetic variants used as instrumental variables should have no pleiotropic effects (111), meaning that the genetic variants should not affect the outcome in any other way than trough exposure X (112).

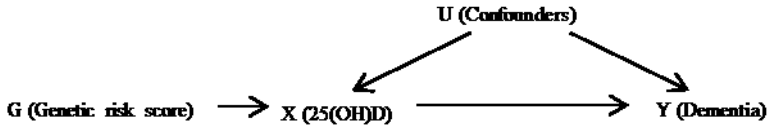

Figure 1. Mendelian randomization design. Published in licentiate thesis 2016.

There is still no convincing evidence that vitamin D supplementation (113-116) has an effect on cognition. A meta-analysis including three interventional studies (n=314) concluded that there was no benefit with supplementation with vitamin D on cognition (113). A randomized study, not included in the meta-analysis, among healthy women, showed that yoghurts fortified with vitamin D (200 IU) and calcium (i.e., 400 mg), taken twice a day for three months, maintained global function compared to women in the placebo group (117).

The rationale for Paper II was the lack of studies on vitamin D intake in relation to incident dementia, the conflicting results from studies with long-term follow-up on the association between plasma 25(OH)D and dementia, and few studies with genetic risk score for vitamin synthesis and dementia.

Diet and PD

The relationship between diet and risk of PD is unclear (118). Previous studies have suggested an association between high consumption of dairy products, especially milk consumption, and increased risk of Parkinson's disease. However, associations between fermented milk consumption and associations with Parkinson's disease have been less studied. A high intake of milk (>473 mL) compared with no milk intake was associated with a 2.3-fold excess risk of PD in 7504 men (including 128 PD cases diagnosed over 30 years of follow-up) in the Honolulu Heart program (119). Results from the Cancer Prevention Study II Nutrition Cohort in the U.S, where 388 out of 130,864 participants

were identified with PD, also found that milk consumption was positively associated with PD risk, but found no association with yogurt consumption (120). High milk consumption was associated with an increased risk of PD in women but was not significantly associated with PD in men in a Finnish cohort (121). No association was found between fermented milk and PD. The cohort was followed-up for 41 years and consisted of 4439 participants where 85 participants were identified with PD (121). In a Greek cohort in which 88 out of 25,407 participants were identified with PD during follow-up, consumption of milk but not yogurt or cheese was associated with incident PD (122). Additionally, milk but not yogurt consumption was associated with PD risk among women and men in the Nurses' Health Study and the Health Professionals Follow-up Study including 129,346 participants of which 1036 were identified with PD during follow-up (123). A meta-analysis including these prospective studies reported a 56% higher risk of PD among those in highest category of milk consumption compared with those in the lowest category of milk consumption (123). In most of these studies, except Nurses' Health Study and the Health Professionals Follow-up Study (123), the number of participants who developed PD during follow-up were few.

In study III, we wanted to investigate associations across the full range of milk and fermented milk intake and not only compare high and low intakes, in a population with a traditionally high intake of milk and fermented milk and also where the number of incident PD cases is relatively high compared with previous studies.

Diet and stroke

The health effects of milk and other dairy products have been widely investigated and discussed (124, 125). A recent meta-analysis observed an 8% decreased risk of stroke with an increment of 200 g per day of milk intake (126). However, several other observational studies did not detect an association between milk consumption and stroke risk (127-130). It is of importance to study associations separately for the different types of stroke since cerebral infarction and hemorrhagic stroke may not have similar pathophysiology (127). Higher milk intake was associated with a lower risk of cerebral infarction (127, 131, 132) whereas no or inverse associations were found between milk intake and hemorrhagic stroke (127, 133, 134). Fermented milk intake was associated with both a lower risk of total or fatal stroke in a dose response meta-analysis (131) and no association was seen between yogurt intake and ischemic stroke (135). The studies on milk and fermented milk have been conducted in different parts of the world and intakes of milk and fermented milk vary between the populations. A high intake in one population can represent a low intake in another population and consequently the reference categories differ between studies and may thus generate different results. Differences in results could also be due the fact that milk and fermented milk such as yoghurt

and sour milk have been studied together and not separately. Few studies have investigated how milk and fermented milk intake are associated with hemorrhagic stroke. In 2012, associations between milk intake and total stroke, cerebral infarction or hemorrhagic stroke were examined in the Swedish cohorts SMC and COSM. No associations were found between milk intake and total stroke, cerebral infarction or hemorrhagic stroke during the mean follow-up of 10.2 years (136). We had the opportunity to re-investigate these potential associations in SMC and COSM, now also including time updated information of both milk and fermented milk consumption, and risk of total stroke, cerebral infarction, and hemorrhagic stroke in a population with traditionally high consumption of milk and fermented milk.

Aims

The overall aim of this thesis was to investigate whether various aspects of diet are associated with common disorders and diseases in the brain.

The specific aims were:

Paper I:
To explore associations of the Healthy Diet Indicator, a Mediterranean-like diet, and a Low Carbohydrate High Protein score dietary pattern with incidence of AD, all-type dementia, and all-type cognitive impairment in a cohort of 70-year-old Swedish men.

Paper II:
To examine whether vitamin D intake, plasma 25-hydroxyvitamin D, and a genetic risk score for vitamin D synthesis are associated with incident AD, vascular dementia, all-cause dementia, and performance in the Mini-Mental State Examination in Swedish elderly men.

Paper III:
To investigate whether milk and fermented milk intakes are associated with incident PD in cohorts of Swedish women and men.

Paper IV:
To assess potential associations of time-updated information on milk and fermented milk consumption with risk of total stroke, cerebral infarction, and hemorrhagic stroke in a Swedish population.

Methods

Study populations

The first two papers are based on data from the Uppsala Longitudinal Study of Adult Men (ULSAM, described in detail at http://www.pubcare.uu.se/ULSAM/) (137, 138). Paper III and IV are based on data from the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM) (139) which are included in the National Research Infrastructure SIMPLER (Swedish Infrastructure for Medical Population-based Life-course Environmental Research; www.simpler4health.se).

The Uppsala Longitudinal Study of Adult Men (ULSAM) cohort

The ULSAM cohort was initiated in 1970 and the aim was to identify risk factors for cardiovascular disease. All men, born in 1920-24 living in the municipality of Uppsala were invited to attend the health survey. In this first investigation, 2841 men were invited and 2322 agreed to participate. The men have been reinvestigated regularly at the approximate ages of 60, 71, 82, 88, and 93 years. The third investigation which was conducted in 1991-95 serves as baseline for Paper I and II. The mean age of the men was then 71 years old. All survivors from the first investigation and still living in Uppsala were invited (n=1681) and 1221 men agreed to participated. Included in the investigations were anthropometric measurements, blood sampling, cognitive tests, medical and lifestyle questionnaires, and a food record. A total of 1138 out of 1221 (73%) recorded their food intake for seven days.

Swedish Mammography Cohort (SMC)

In 1987–90, all women, born in 1914–1948, and living in the counties of Västmanland, Uppsala were invited to participate in the population-based mammography screening program. Included with the invitation was a questionnaire about family history of breast cancer, marital status, age at first childbirth, diet- and alcohol intake, education, weight, and height. The initial aim was to study the relations between dietary intake and breast cancer risk. A total of 90,303 women were invited and 66,651 (74%) responded to the first questionnaire. After exclusion of those with an incorrect or missing personal identity number, history of cancer (except non-melanoma skin cancer), death

before baseline (1 January 1998), participants with an implausible energy intake (defined as 3 standard deviations from the $\log_e$-transformed mean energy intake) the cohort consisted of 61,433 participants. Further, we excluded more cases of cancer due to our code for cancer diagnosis compared to earlier studies, and thus the cohort consisted of 61,137 participants.

In 1997, a second questionnaire was sent to those women who were still alive and living in the same area (n=56,030). The response rate was 70%. This questionnaire was expanded with questions about smoking and snuff habits, physical activity and exercise, sleep habits, waist and hip circumferences, body weight across the life course, occupation, dietary supplements, diseases, menopause, contraceptives, and use of hormones. Characteristics, including age distribution, body mass index (BMI) and educational level, of the SMC cohort are considered comparable to the Swedish population (139).

A third questionnaire, not including diet but including questions about general health, disease diagnoses, body weight, height, waist and hip circumferences, dental health, medication use, sleep habits, urine and bowel habits, family history of selected diseases, stress, and social support, was sent out in 2008 to those still alive who had participated in the survey in 1987 (n=48,263). The response rate was 63% (n=30,621). A fourth questionnaire about lifestyle including questions on diet and alcohol intake, physical activity, smoking habits, sun habits and intake of dietary supplements was sent out in 2009 to those who completed the questionnaire in 2008 (n=30,134). The response rate was 84% (n=25,332) in this fourth survey (139).

Cohort of Swedish Men (COSM)

COSM was initiated in 1997 and is a population-based cohort. The aim was to study relations between diet and lifestyle and chronic diseases. All men, born in 1918–1952, and residing in the counties of Västmanland and Örebro (n=100,303) received a lifestyle questionnaire by mail and 49% responded (n=48,850). Except for some gender-specific questions such as questions about urinary tract symptoms (International Prostate Symptom Score [I-PSS]) the questionnaire was identical to the questionnaire used in SMC 1997. After exclusion of those with an incorrect or missing personal identity number (n=297), history of cancer (n=2592, except non-melanoma skin cancer), death before baseline (before 1 January 1998, n=55) the cohort consisted of 45,906 participants. The characteristics of the participants in COSM were similar to the Swedish population regarding age distribution, BMI and educational level (139).

In 2008, the same questionnaire (except for some gender-specific questions) as used in SMC in 2008 was sent out to all still living COSM participants (n=37,861) and 78% responded. Those who completed the questionnaire

in 2008 received the same questionnaire as the participants in SMC 2009 (except for gender-specific questions). A total of 29,068 questionnaires were sent out and the response rate was 90% (n=26,161).

Exposures

Dietary record Paper I and II

In Paper I and II the participants recorded their food intake for seven consecutive days using a pre-coded optically readable food record (ORFR) (140, 141). The participants were instructed by a dietitian or a nurse on how to perform the dietary record. The ORFR contained pre-printed dishes and food items. Portion sizes had to be filled in, either as household measurement or choosing from four pre-printed portion sizes illustrated by photographs. Also, the amount of bread spread used was illustrated by photographs. Foods and drinks that were not pre-coded could be written as free text. The food record was read by an optical reader (Kaiser OMR 32) and free text was manually typed into a computer. A computerized dietary assessment program (142) with information from the National Food Administration food composition database (SLV version 1990) was used to calculate each participant's daily food, energy, and nutrient intake. The ORFR was validated against a seven day open ended weighted record (WT) in 73 participants in the ULSAM cohort. For energy and energy-yielding nutrients the Spearman correlation coefficients between the two methods intakes were moderate to high i.e. 0.4 to 0.6 (140). Protein intake obtained from ORFR and WT were compared to calculated protein intake from 24-hour urine nitrogen excretion. Both dietary assessment methods showed a lower intake of protein compared to the calculated protein intake from the 24-hour urine nitrogen excretion. The agreement between the methods was acceptable (140). Average daily vitamin D intake was 6.2 (± 2.5) µg measured with the ORFR and 7.1 (± 2.3) µg measured with the WR.

Dietary patterns

We calculated adherence to a modified version of HDI (55, 62, 143). In the original HDI, nuts and seeds are included but these foods were excluded due to low intakes in our population. We also replaced complex carbohydrates with total carbohydrates and included a negative score for those with intakes of sucrose above the desirable value. Pulses were included in vegetables. Depending on the nature of the nutrient of the component included in the score, dietary variables were adjusted for energy intake either by the residual method (52) (variables in g/day) or as nutrient densities (energy percent or g/MJ). HDI can take a value of −1 to 8 p and if the participants intake were within the

desirable range, they scored 1 point (p) for the following nutrients and foods; saturated fatty acids (SFA), poly unsaturated fatty acids (PUFA), protein, total carbohydrates, fiber, fruit and vegetables, cholesterol and fish. If the intake was outside the desirable range or cut off, they scored 0 points, except for sucrose where an intake above the cut off value yielded -1 p, otherwise 0 p. The cut offs were based on the intake in the current population. The adherence was classified as low (-1 to 1 p), medium (2-5 p), or high (6-8 p).

We calculated adherence to a modified Mediterranean score (57) that was modified to suit Swedish dietary habits (62). As in the HDI, pulses were included in vegetables and nuts and seeds were excluded due to low intakes. Potatoes were included with cereals due to high intakes and thus contributing to complex carbohydrate intake. During the time of the dietary investigation, consumption of olive oil was low and saturated fatty acids (SFA) and monounsaturated fatty acids (MUFA) had similar food origins in the Swedish diet. MUFA were therefore replaced by polyunsaturated fatty acids (PUFA). We calculated the median intake for all dietary variables (except for alcohol consumption) of the population. An intake above the median intake for favorable foods (PUFA/SFA, vegetables and legumes, fruit and berries, cereals and potatoes, and fish) yielded 1 p and an intake above the median for unfavorable foods (meat and meat products, and milk and milk products) yielded 0 p. An alcohol consumption between, 10–50 g/d yielded 1 p, given that the ratio of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) was less than 2. This was done to reflect moderate alcohol intake and avoid a favorable score for heavy drinkers. The mMDS score could take a value of 0–8 point. Individuals were group as low (≤2 p), medium (3–5 p), or high (≥6 p) adherent to the mMDS.

We calculated adherence to the LCHP diet by dividing each participant's intake of carbohydrates and protein into deciles. Carbohydrate intake gave points from 10 to 1 where the highest intake gave the lowest score. Conversely, protein intake gave points from 1 to 10 where the highest intake gave the highest score (62, 63, 144). These points were added and the LCHP score could thus take a value from 2–20. Adherence was classified as low (≤6 p), medium (7–15 p) or high (≥16 p).

The cutoffs for adherence to each dietary pattern were chosen in order to compare extreme groups of comparable and reasonable sizes (62) and the low adherent group served as reference in analyses. The continuous variables correspond to a 2-point increase in the HDI and mMDS scores and a 4-point increase in the LCHP score.

Vitamin D

Vitamin D intake

Vitamin D intake was assessed based on the food records in ULSAM, as described above. Information on use of vitamin D supplements, both dosage and

frequency, were taken from the baseline questionnaire. We added supplementary vitamin D (n=37) to dietary vitamin D to obtain total vitamin D intake.

Plasma 25(OH)D

Plasma samples were drawn after an overnight fast and stored at -70°C until analysis. The maximum storage time was 15 years (137), and 25(OH)D has been proven to be stable in stored plasma (145). We measured 25(OH)D with HPLC atmospheric pressure chemical ionization-mass spectrometry (HPLC–mass spectrometry) (Vitas, Norway) (146, 147). We used total 25(OH)D, including both $25(OH)D_3$ and $25(OH)D_2$ since concentrations of $25(OH)D_2$ were low. The coefficient of variation was 7.6% at 47.8 nmol/L and 6.9% at 83.0 nmol/L for $25(OH)D_2$ in the interassay analysis (146).

Genetic risk score (GRS)

Two single nucleotide polymorphisms in genes involved in vitamin D synthesis and with no known pleotropic effect (148, 149) were selected to create a genetic risk score (GRS). To create the GRS, we added the number of alleles that were associated with higher 25(OH)D concentrations in two single nucleotide polymorphisms: rs12785878 in the 7-dehydrocholesterol reductase gene (*DHCR7*; the T allele is associated with higher 25(OH)D) and rs12794714 in the vitamin D 25-hydroxylase gene (*CYP2R1*; the G allele is associated with higher 25(OH)D) (148, 149). Thus, a higher GRS score is associated with higher 25(OH)D concentrations. We had information on single nucleotide polymorphisms in 1087 participants from the examination in 1991–1995.

Food frequency questionnaire Paper III and IV

We collected information about usual dietary intake with a validated food frequency questionnaire (FFQ). The FFQ was sent out to participants to collect information about usual dietary intake during the past 6 months for FFQ1 in 1987 and during the past year for FFQ2 in 1997, and FFQ3 in the 2008/2009 survey. FFQ1 included 67 items of foods and beverages. In the next surveys, the FFQ was expanded with additional food and beverage items (FFQ2 contains 96 items, and FFQ3 contains 132 items) (150). For each food item, the participants could choose how often they consumed each food; 0, 1-3 times per months, 1-2, 3-4, 5-6 times per week, or 1, 2, or 3+ times per day (or 4+ in FFQ1). The FFQ also included open questions for some commonly consumed foods and beverages such as bread, coffee, tea, soft drinks and dairy foods. Participants recorded their daily consumption (number of 200 ml glasses) of skimmed milk (≤0.5% fat), reduced-fat milk (1.5% fat), regular milk (3% fat or higher), reduced-fat yogurt and sour milk (0.5% fat), and regular fat yogurt and sour milk (3% fat) (151). We summed the number of glasses per day for milk and fermented milk separately. In the first FFQ1 used in the SMC baseline survey, frequencies of milk and fermented milk were

summed up separately and multiplied with age-specific portion sizes (152). Missing information on milk and fermented milk were treated as zero consumption in the main analyses (153, 154).

We calculated the average energy and nutrient intake per day by multiplying the frequency of each food item by the nutrient or energy content in age-specific portions of each food, obtained from the Swedish National Food Agency database (155).

The FFQ was validated, in a randomly selected subsample of 129 women from SMC, against four 7-day weighted food records completed every third month. The Pearson correlation coefficient for milk intake was approximately 0.7 and for sour milk/yogurt for 0.7 between FFQ and the food records (136, 152) (A Wolk, unpublished data, 1992). Furthermore, the FFQ was validated against fourteen 24-h recall interviews in 248 Swedish men in Uppsala County. The Spearman rank correlation coefficient was 0.65 for macronutrients and 0.62 for micronutrients (0.77 for calcium for which milk is a major source) between FFQ and the 24-h recall interviews (156). The reproducibility of FFQ was also investigated among these men and the reproducibility between FFQs investigated with one year apart indicated a high degree of reproducibility (intraclass correlation for macronutrients was approximately 0.7) (156).

Outcome

We used different approaches for assessment of main outcomes. In Paper I and II, all participants' medical records were reviewed to identify cases of dementia and time of diagnosis. In addition, cognitive function was measured in some participants. In Paper III and IV, we used data from Swedish registers to identify cases of PD and cases of stroke and time for the diagnosis.

Case ascertainment and follow-up, Paper I and II

Cognitive function was screened by Mini-Mental State Examination (MMSE) (17) at baseline (age 71) and at the follow-up examinations at the age of 77 years and 82 years. MMSE is a commonly used screening tool for cognitive impairment and includes 20 questions covering areas on temporal and spatial orientation, immediate and delayed memory, attention and calculation, language, ability to follow commands and figure coping. The maximum score is 30 and a score $\leq$24 has been used as a cut off for indication of pathologic cognitive impairment (17, 157). If the participants had low scores, indicating cognitive impairment, they were recommended to make an appointment at the Memory Clinic, Uppsala University Hospital for a memory assessment. The vast majority of all incident cases of dementia in ULSAM were captured at the Geriatric Memory Clinic or at the Geropsychiatric Department, Uppsala

University Hospital. Results from the examination and diagnosis were registered in the patients' medical record. Two experienced geriatricians reviewed all participants' medical records to track all incident cases of dementia (until December 2005 for Paper I and until December 2009 for Paper II), from the Uppsala University Hospital, Uppsala primary care and nursing homes (158). A third geriatrician reviewed the case if the first two disagreed on the classification of the case. AD was defined according to the National Institute of Neurological and Communication Disorders and Stroke and Alzheimer's disease and Related Disorders Association criteria (159) and the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria (160). Vascular dementia was diagnosed according to the criteria of Chui et al. (161), and cases with concomitant AD and vascular dementia were allocated to this group. Cases of dementia without neuroimaging or sufficient clinical details in medical records to set a specific subtype diagnosis were classified as unspecified dementia (158). All type-dementia as in Paper I and all-cause dementia as in Paper II included AD, vascular dementia, frontotemporal dementia, Lewy body dementia, unspecified dementia, and Parkinson disease with dementia. Time of diagnosis was noted and used for time to event analysis.

The stage of manifest dementia is preceded by mild cognitive impairment. In Paper I, we defined the diagnosis all-type cognitive impairment in order to include cases of cognitive decline not fulfilling the dementia criteria. MMSE was measured at baseline (age 71) and at follow-up (age 82 years). All-type cognitive impairment was defined as all-type dementia and/or ≥3 points decline in MMSE over the 12-y period and/or MMSE <25 points at follow up (at the age of 82). In Paper II, cognitive impairment was defined as a decline in the MMSE ≥3 points over the 12-y period or an MMSE score of <25 points at follow-up. Since information on MMSE was incomplete at baseline and at follow-up, we considered all-type cognitive impairment and cognitive impairment as secondary outcomes.

Register data, Paper III and IV

We identified incident and previous PD and stroke cases, until the end of follow-up (i.e., 31 December 2019), by linking participants' national registration number (assigned to each Swedish resident) to the Swedish National Patient Register (NPR) and the Cause of Death Register. The NPR was initiated in the 1960's by the National Board of Health and Welfare and contains information on all patients at public hospitals. The Ministry of Health and Welfare and the Federation of County councils decided in 1984 that all-inpatient (hospital) somatic and psychiatric care in Sweden would be included in the registers. Since 1987, all in-patients are included and from 2001 also outpatient visits to private and public healthcare providers, including doctor (specialist) visits, day care surgery and psychiatric care are included in the NPR (162). Information about patients in primary care is not included. The information in NPR covers

four areas; patient data including personal registration number, sex, and age; geographical data including county council, hospital/clinic and department; administrative data including information such as date of admission and discharge and length of stay, medical data including main and secondary diagnosis (coded according to the Swedish version of International Classification of Diseases; ICD), external cause of injury and poisoning, and procedures. Overall, the NPR has high validity and the coverage of in-patient is almost 100% but a little less for some private clinics (162). The loss of main diagnosis in 2019 for inpatient care was 1.0% and for specialized outpatient care 2.8% (163).

The Swedish Cause of Death Register is administered by The National Board of Health and Welfare and was introduced in its current form in 1952. The register contains information about the causes of deaths in the Swedish population, both living in Sweden and outside of Sweden (164). The cause of death is coded according to the international version of ICD-codes and WHO (164, 165). The completeness of the cause of death is considered very high with a lack of information of cause of death in only 0.9 % of all registered deaths in 2015 (164).

To classify PD, we used the following ICD codes: 332.0 (ICD-9, 1987-96), and G20 (ICD-10, 1997-2014), 350 (ICD-7, 1964-68), 342 (ICD-8, 1969-86). The PD diagnoses from Swedish registers have been validated in a Swedish twin study where the twins were screened for PD. The accuracy for PD diagnoses was 70.8% and sensitivity 72.7% between the registers and the twin PD study (166).

To classify total stroke, we used the ICD-9 codes 430, 431, 433, and 434 and the ICD-10 codes I60, I61, I63 and I64. Total stroke was divided into cerebral infarction (ICD-9 codes 433 and 434, and ICD-10 code I63) and hemorrhagic stroke (ICD-9 codes 430 and 431, and ICD-10 codes I60 and I61).

Assessment of covariates

We used current knowledge and the directed acyclic graph (DAG) method to select covariates (167) (Paper II-IV). DAG is a graphical tool for visualizing and identifying causal relationships and biasing paths for the research question and helps us to understand whether conditioning on a covariate will increase or decrease bias (167, 168).

In Paper I and II, information on possible covariates were collected from baseline examinations, questionnaires, and interviews (1991-1995*)*. Systolic and diastolic blood pressure (in the supine position), blood glucose, serum cholesterol, and body weight and height were measured at baseline. Body mass index (BMI; kg/m^2) was calculated as weight divided by the square of height. Apolipoprotein E (APOE) was genotyped (absence of e4 alleles versus presence of at least one of the e4 alleles) (169) and used in Paper I. Hyperten-

sion was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or treatment with an antihypertensive medication. Hypercholesterolemia was defined as a serum cholesterol concentration ≥6.5 mmol/L or treatment with cholesterol-lowering medications. Diabetes was defined as a fasting plasma glucose concentration >7 mmol/L or treatment with a diabetes medication. From the questionnaires and interviews, we collected information on smoking status (never, former, or current); educational level (low [6–7 y], medium [high school], or high [college or university]); health status; living conditions, and physical activity level (sedentary, moderate, regular, or athletic) (42). Season of blood collection was defined as summer (May 1 to October 31) or winter (November 1 to April 30) and used in Paper II. Energy intake was calculated from the 7-day dietary record. Alcohol consumption was categorized as abstainers, consumers, or daily consumers.

In Paper III and IV, information on covariates was collected from the questionnaires and from the National Patient Registry. Smoking status, walking/bicycling in the past year (never/seldom, < 20 min/day, 20-40 min/day, 40-60 min/day, 1-1.5 hours/day, >1.5 hours/day), exercise in the past year (< 1 hour/week, 1 hour/week, 2-3 hours/week, 4-5 h/week, >5 h/week), BMI (from self-reported height and weight), educational level, living alone, hypertension, hypercholesterolemia, diabetes mellitus, supplement use, total energy intake, consumption of coffee, soft drinks and juice, alcohol, fruits and vegetables, processed meat, and total- and saturated fat were all collected from questionnaires. From the National Patient Registry, we retrieved information on inpatient treatment to be used in the Charlson's weighted comorbidity index (170, 171). Questions on smoking, physical activity, supplement use, hypertension, hypercholesterolemia, and diabetes were not included in the first investigation in 1987 and we therefore used information on these variables from the 1997 investigation.

Ethics

Ethical approval was sought and approved by the Regional Ethical Review Board in Uppsala or Stockholm for all studies in the thesis. The studies on PD and stroke were additionally approved by the Swedish Ethical Review Authority. All research was performed in accordance with the declaration of Helsinki. Participation in the studies was voluntary and the participants were free to withdraw the study at any time. All participants gave their written informed consent.

Statistical analysis

For all main outcomes in this thesis, we used time to event analysis. Time at risk from the decided baseline date until the date of the first diagnosis, date of death, or end of follow-up, were calculated for all outcomes except for all-

type cognitive impairment and cognitive impairment. In the main analysis, we used Cox proportional hazards regression to estimate hazard ratios (HR) with 95% confidence intervals (CI) for the association between exposure and outcome. In this model it is assumed that the relative hazards are constant over time which means that what affects the hazard does this with the same ratio at all times, the hazards are proportional (172). The proportional hazard assumption can be checked in different ways; by visual inspection of Kaplan-Meier curves and log-log plots (used in Paper I-III) or by testing of Schoenfeld residuals with graphical confirmation of the result (used in paper IV).

We used logistic regression to estimate odds ratios (OR) with 95% CI between dietary intake and all-type cognitive impairment in Paper I and between vitamin D and cognitive impairment in Paper II. Logistic regression was used because there was no information on exact date for all-type cognitive impairment, because dementia diagnosis and results from MMSE were pooled together. We chose to use logistic regression analysis for cognitive impairment in Paper II for the same reason.

We investigated potential nonlinear trends between exposure and the main outcomes by restricted cubic spline Cox regression with three knots placed at the 10th, 50th, and 90th percentiles of the distribution of the exposures (Paper II-IV) (173). In Paper I, non-linearity was tested by introducing a square term of the exposure in the models.

All analyses were carried out in Stata 11 to Stata 15 (StataCorp, College Station, Texas, USA).

Missing data

Complete case analysis including only available data on exposure, outcome and covariates was used in the analysis in Paper I. In Paper II, we used the last value carried forward technique for covariates with missing information. In Paper III and Paper IV, missing information on covariates were imputed by multiple imputation using chained equations (twenty imputations).

Paper I

The study population was based on 1138 men with complete dietary records from ULSAM. Participants with self-reported diabetes were excluded in paper I (n=67) due to possible recent dietary changes after dietary advice. Also extreme over-and under reporters of energy intake were excluded according to Willet's recommendations (52). Participants with a reported energy intake >4200 kcal/d (n=1) and <800 kcal per day (n=4) were excluded. After these exclusions we calculated adherence to the dietary patterns in the remaining men (n=1066). We further excluded participants with diagnosed dementia at baseline and those with weight loss exceeding 10% between 60–70 years of age due to potential serious illness before baseline. The final study population

included 1038 men. According to AD criteria, stroke cases with aphasia cannot be diagnosed as AD and we therefore censored stroke cases with aphasia in the main analysis and excluded those in the logistic regression analysis (Figure 2). In the logistic regression with all-type cognitive impairment as outcome, participants with stroke (with aphasia), those who died without a dementia diagnosis during follow-up, or were alive with no dementia diagnosis but not participating in the follow-up at age 82 were excluded; 564 individuals remained (143 with all-type dementia, 55 with cognitive impairment, and 366 with no cognitive impairment).

We adjusted for energy intake (continuous) in model 1. In model 2, we adjusted for energy intake (continuous), educational level, physical activity, smoking, single household, and apolipoprotein E (APOE) genotype (absence of e4 allele versus presence of at least one e4 allele).

In sensitivity analyses, we repeated all analyses in a subpopulation (n=654) defined according to the Goldberg's cut-off for mis-reporters of energy intake (Figure 2) (62, 174). This is a stricter definition of under- and overreporters of energy intake. In brief, reported energy intake (EI) is compared to energy expenditure (EE). If the person is weight stable, then EI= EE. EE constitutes of the basal metabolic rate (BMR) multiplied by the physical activity level (PAL). This can also be expressed as EI:BMR=PAL. PAL from EI:BMR can then be compared to expected PAL. In reality, PAL from EI:BMR and expected PAL cannot be exactly similar due to measurement errors and therefore confidence intervals have to be calculated. In the Goldberg method, cut offs for lower and upper limits of reasonable energy intake is created. In this study, BMR was calculated by Schoenfeld's equation based on age, sex, height and weight (175, 176). The PAL value used in the calculation for lower and higher cut offs are based on physical activity questionnaire and modified by Sjögren et al (62) (sedentary PAL 1.4, moderately active PAL 1.5, regularly active PAL 1.6, and athletic PAL 1.7). For each participant, an individual 95% CI for PAL (EI:BMR) was calculated and compared to the reported EI:BMR. We compared the reported EI:BMR with the individual calculated 95% PAL (EI:BMR) value. If the reported EI:BMR was not within the upper or lower limit they were classified as low or high energy reporters and were excluded.

Paper II

The study population consisted of 1182 men in ULSAM with plasma 25(OH)D concentrations after exclusions of dementia diagnosis or stroke with aphasia (Figure 2) before baseline and within two years after baseline (n=12). In the analysis of dietary vitamin D intake, 1101 participants were included after exclusions of extreme reported energy intakes (n=5). For the analysis of genetic risk score, 1087 men were eligible. We analyzed the associations of dietary vitamin D and plasma 25(OH)D concentrations, both as continuous variables and predefined scores, in relation to AD, vascular dementia, and all-

cause dementia. Dietary vitamin D intake was divided into tertiles: ≤4.7, > 4.7-6.5, and >6.5 μg/d. The predefined categories for plasma 25(OH)D were ≤50, >50–75, and >75 nmol/L. The highest category was used as reference category in the analysis. The GRS was analyzed as a continuous variable. We used Cox proportional hazards regression in the analysis of AD, vascular dementia, and all-cause dementia. Measurements of cognitive impairment was available in 488 men and logistic regression analysis was used to analyze the association between vitamin D and cognitive impairment. Potential nonlinear trends were investigated by restricted cubic splines with three knots placed at the 10th, 50th, and 90th percentiles of the distribution (43). We used 5 mg/d as the reference point for dietary vitamin D and 50 nmol/L as the reference point for plasma 25(OH)D concentrations. In the analysis of vitamin D intake, we adjusted for age and energy intake in model 1. Model 2 further included BMI, education, physical activity, and smoking. Model 3 included covariates in model 2 and diabetes, hypertension, and hypercholesterolemia (as categorical variables). In the analysis of plasma 25(OH)D, we used three models for adjustments. Model 1 included age and the season of blood collection. Model 2 further included BMI, education, and physical activity. Model 3 included covariates in model 2 and smoking, diabetes, hypertension, hypercholesterolemia (as categorical variables), vitamin D supplements, and alcohol intake (yes or no). In the analysis of GRS, no adjustments were made in model 1. Model 2 included age, season of blood collection, BMI, education, and physical activity.

Paper III

Paper III included participants from SMC and COSM and baseline for this study was the 1997 survey. The study population consisted of 81,915 participants (36,664 women and 45,271 men) after exclusions of women and men with an incorrect or a missing personal identity number, those with a history of cancer or death before baseline, implausible energy intake (defined as 3 standard deviations from the log-transformed mean energy intake in women and men separately) and a PD diagnosis before baseline (Figure 3). Milk and fermented milk intakes were assessed with FFQ and PD cases were identified through the Swedish registers as described above. In the main analyses, time at risk of PD for each participant was calculated from baseline (January 1, 1998) until the date of PD diagnosis, date of death, or end of follow-up (December 31, 2014), whichever came first. Cox proportional hazards regression models with age as time scale was used to estimate HRs and 95% CIs for categories of milk (Q1; <40 mL/day, Q2; 40–159 mL/day, Q3; 160–200 mL/day, Q4; >201–400 mL/day, Q5; >400 mL/day) and fermented milk intake (Q1; <40 mL/day, Q2; 40–159 mL/day, Q3; 160–200 mL/day, Q4; >201 mL/day). The category with the lowest intake was used as reference. Potential nonlinear trends between milk and fermented milk intake and incident PD

were assessed by restricted cubic splines as described above. In the main model, we adjusted for sex through stratification, smoking status, (never, former with <20 pack-years, former with ≥20 pack-years, current with <20 pack-years, or current with ≥20 pack-years), educational level (≤9 years, 10–12 years, >12 years, or other), alcohol and coffee consumption (both continuous), total energy intake (kcal/day; continuous), BMI (continuous), physical activity (walking/bicycling and exercise during the previous year; categorical) and living alone (yes/no), total fruit and vegetable intake, vitamin and mineral supplement use (yes/no). The model further included fermented milk (in analyses of milk) or milk intake (in analyses of fermented milk).

Paper IV

Paper IV included participants from SMC and COSM. Information on milk and sour milk, and yogurt consumption was assessed in 1997 and 2008/2009 and we used the information to time update our analysis on exposure and covariates. We used information from the 1987-90 survey in SMC in sensitivity analysis. The study population in the main analysis included 79,618 participants (35,892 women, 43,726 men) after exclusions of participants with an incorrect or a missing personal identity, those with a diagnosis of stroke or cancer or who died before baseline (those who had answered the FFQ but died before the decided starting date for every baseline), and those with implausible energy intakes, defined as 3 standard deviations from the log-transformed mean energy intake in women and men separately (Figure 4). Further, we excluded 567 participants with an implausible energy intake defined as 3 standard deviations from the loge-transformed mean energy intake. Those with a reported intake <861 kcal/day and >7311 kcal/day were excluded thus leaving 45,339 participants in the cohort.

Time at risk was calculated, in main analyses for the pooled cohorts and for each cohort (SMC, and COSM) separately, from January 1st 1998 until the date of the first stroke diagnosis, date of death, or end of follow-up (December 31st 2019), whichever came first.

Potential nonlinear associations of milk and fermented milk intake with incident total stroke, cerebral infarction, and hemorrhagic stroke were assessed by restricted cubic spline Cox proportional hazards regression. As reference, we used 100 g/d and we derived HR estimates based on the spline curve at intakes of 200 g/d, 400 g/d, 600 g/d, and 800 g/d. In model 1 we adjusted for sex through stratification and age (using splines). In model 2 we adjusted for sex, age, educational level (≤9 years, 10–12 years, >12 years, or other), living alone (yes/no), smoking status (current, former, never), physical activity (walking/bicycling and exercise during the previous year; categorical), BMI (continuous), history of hypertension (yes/no), hypercholesterolemia (yes/no), and diabetes mellitus (yes/no), coronary heart disease, Charlson's weighted comorbidity index (continuous), vitamin- and mineral supplement use

(yes/no), and intakes of total energy (kcal/day; continuous), fruits and vegetables (servings/d; continuous), processed meat (servings/day; continuous), soft drinks and juices (servings/day; continuous), alcohol (g/day; continuous), coffee (cups/day; continuous), fermented milk (in analyses of milk; categorical) or milk (in analyses of fermented milk; categorical), total fat (g/day continuous), and saturated fat (g/day continuous). In sensitivity analysis we also investigated associations in SMC with start in 1987-90 and updated information as described above.

Time updated information

In paper IV, information on exposures and covariates were available for SMC from the 1987-90, 1997, and 2008/2009 investigations. For COSM, information on exposures and covariates were obtained first in 1997 and then in 2008/2009. Usually, only the first time point for exposure information is used in analysis. In time-updated analyses, the exposure information (milk and fermented milk intake) is updated when new information is available. Each participant's follow-up time is split into periods and both exposure and covariates are updated at the beginning of each period. For the main analysis, this was done once; in 2009. For the SMC sensitivity analysis, it was done twice; in 1997 and 2009. As usual, each participant is followed until an event (stroke), censoring or end of follow-up. This allows for taking changes in exposures into account in the analysis.

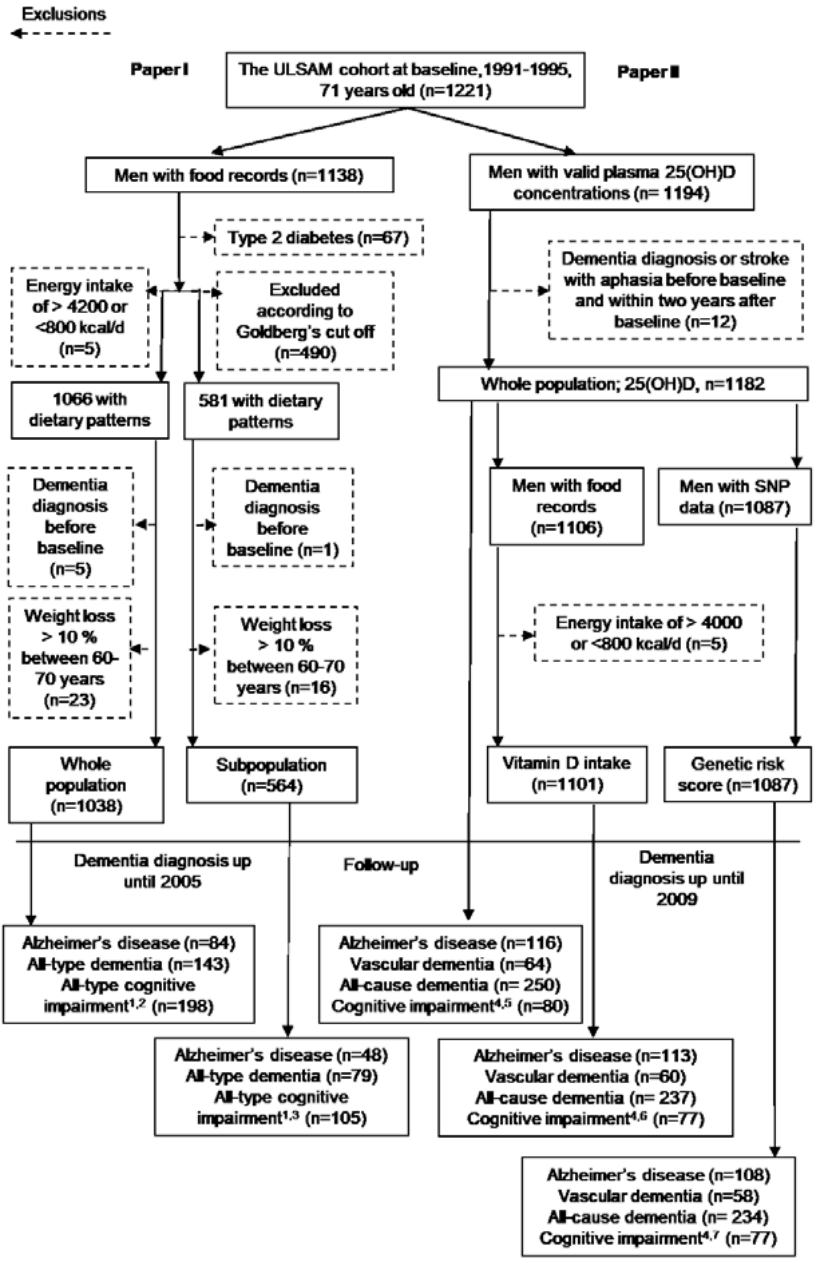

Figure 2. Flow chart for exclusions and outcomes, Paper I and Paper II.

[1]All type dementia and/or ≥3 points decline in MMSE and/or < 25 points at follow up. [2]143 men with all-type dementia and 55 with cognitive impairment as determined by MMSE. 366 individuals had no cognitive impairment according to MMSE. [3]79 men with all-type dementia and 26 with cognitive impairment as determined by MMSE. 222 individuals had no cognitive impairment according to MMSE. [4]≥3 points decline in MMSE and/or < 25 points at follow up. [5]The analysis included 488 men. [6]The analysis included 473 men. [7]The analysis included 471 men.

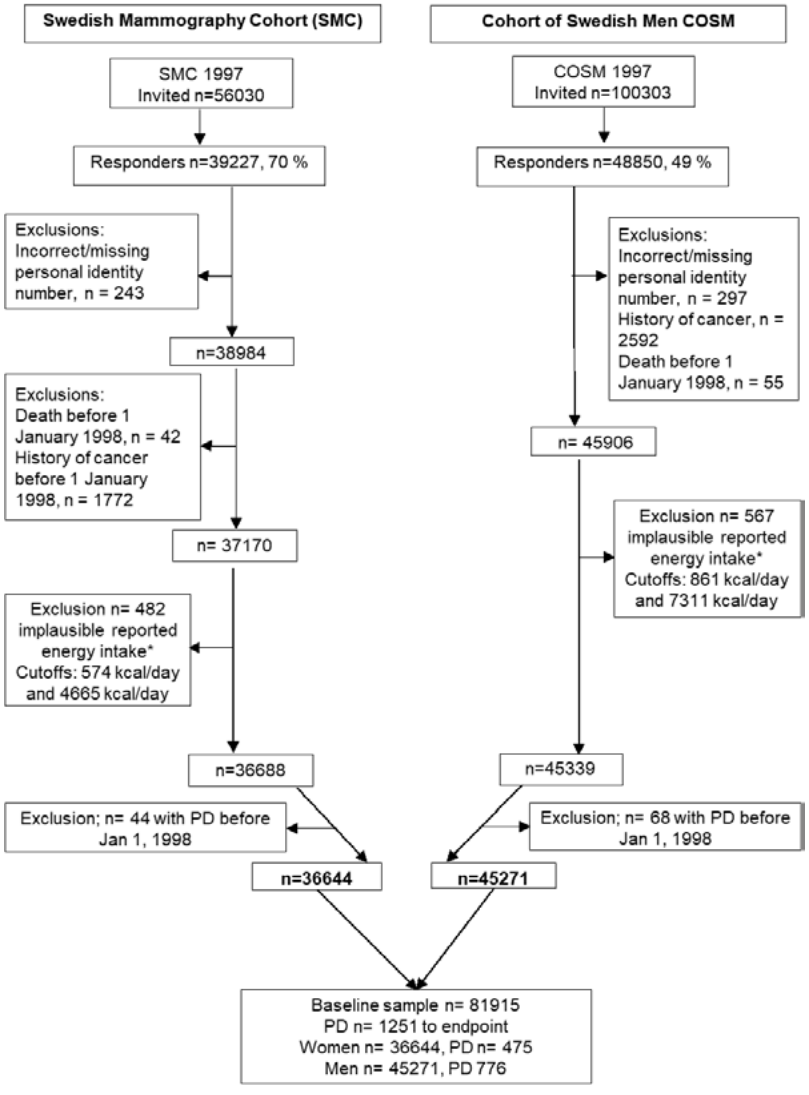

Figure 3. The Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM), paper III.

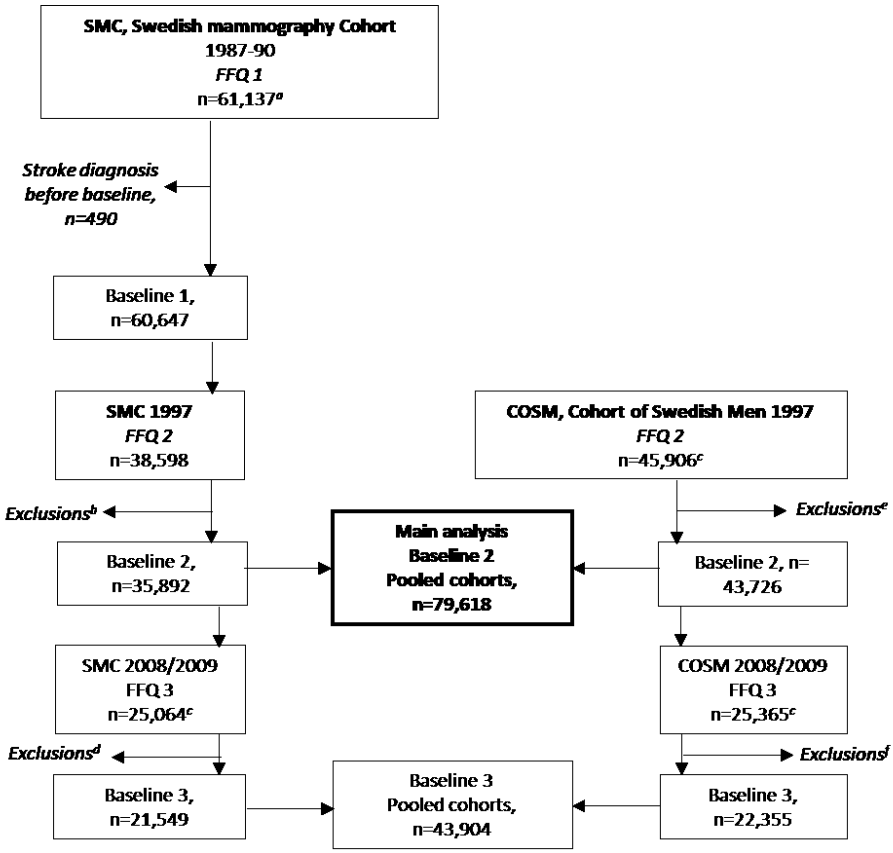

Figure 4. The Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM), paper IV.

Food Frequency questionnaire; (FFQ)
[a]Cohort after exclusions of incorrect or missing personal identity number, history of cancer, and implausible reported energy intake.
[b]Exclusions; Death before January 1st 1998, n=41; history of cancer before January 1st 1998, n=1608; implausible reported energy intake (cutoffs: 574 kcal/day and 4699 kcal/day), n=476; stroke diagnosis before January 1st 1998, n=581.
[c]Number of individuals after exclusions of death before baseline.
[d]Exclusions; History of cancer diagnosis before April 14th 2009, n=2403; implausible reported energy intake (cutoffs: 610 kcal/day and 5315 kcal/day), n=212; stroke diagnosis before April 14th 2009, n=900.
[e]Exclusions; History of cancer January 1st 1998, n=187; implausible reported energy intake (cutoffs: 862 kcal/day and 7303 kcal/day) n=562; stroke diagnosis before January 1st 1998, n=1431.
[f]Exclusions; History of cancer diagnosis before April 14th 2009, n =1742; implausible reported energy intake (cutoffs: 834 kcal/day and 7371 kcal/day) n=183; stroke diagnosis before April 14th 2009, n=1085.

Results

Baseline characteristics of the study populations are presented in Table 1.

Table 1. Baseline characteristics of the study populations. Paper I and Paper II included participants from the Uppsala Longitudinal Study of Adult Men (ULSAM). Paper III and Paper IV included participants from the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM).

Characteristics	Paper I	Paper II	Paper III	Paper IV
Number	1038	1182	81915	79618
% Women	0	0	44.7	45.1
Age, years	71.0 (0.6)	71.0 (0.6)	61.5 (9.5)	61.3 (9.5)
Weight, kg	80.3 (11.2)	80.4 (11.5)	75.2 (13.1)	74.9 (23.1)
Height, cm	174.9 (5.8)	174.8 (6.0)	172 (8.9)	171.3 (8.9)
Body mass index, kg/m^2	26.2 (3.3)	26.3 (3.4)	25.4 (3.6)	25.4 (3.7)

Mean (SD) if not otherwise stated.

Paper I

The whole population consisted of 1038 participants and the mean age was 71 years. Participants with low adherence to HDI and mMDS, had lower education and were more likely to be current smokers compared to those with high adherence to these dietary patterns. Those with low adherence to LCHP compared to high adherers had a lower BMI, were less frequently current smokers, and had lower attained educational level. There were no major differences in energy intake or other baseline characteristics between low, medium, or high adherers in any of the dietary patterns (except higher C-reactive protein for high adherers to LCHP).

Those with high adherence to LCHP had higher intakes of meat products, cheese, milk products, lower intakes of fruit and berries, lower intakes of jam, soda, dessert and cake than low adherers to LCHP. Total fat intake was also higher in high adherers to LCHP as well as intakes of SFA, PUFA, and MUFA compared to low adherers.

The mean follow-up time was 11.6 years, with 10,940 person-years at risk, and during this period we identified 84 men with AD, 143 men with all-type dementia, and 198 men with all-type cognitive impairment. We observed no associations between adherence to HDI and any of the outcomes studied or

with adherence to a Mediterranean-like diet and AD or all-type dementia (Figure 5). An inverse association was observed between adherence to mMDS and all-type cognitive impairment and a direct association was observed between adherence to LCHP and all-type dementia, although the CIs included 1. The adjusted OR for all-type cognitive impairment was 0.82 (95% 0.65, 1.05) for mMDS (continuous) adherence and the adjusted HR for all-type dementia was 1.16 (95% CI 0.99, 1.37) LCHP (continuous) adherence.

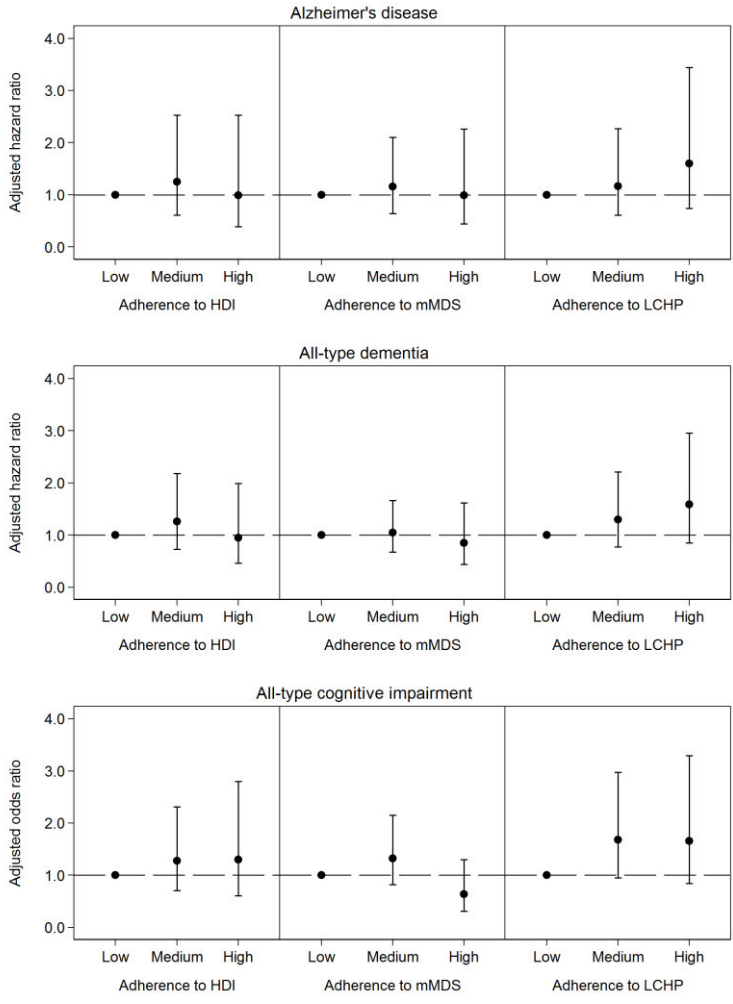

Figure 5. Risk estimates for Alzheimer's disease, All-type dementia, and All-type cognitive impairment in relation to adherence to each diet in the whole population. Published in licentiate thesis, 2016.

The subpopulation according to the Goldberg cut off consisted of 564 participants and the number of cases was reduced to almost half of the original population (Figure 6). We identified 44 men with AD, 79 men with all-type dementia, and 105 men with all-type cognitive impairment. No association was found between adherence to HDI and any of the outcomes. There was an inverse association between adherence to mMDS and AD and all-type dementia but the CIs included 1. The risk estimates for LCHP and All-type dementia and all-type cognitive impairment were lower and the CIs wider in this subpopulation compared to results from the whole population (Figure 6).

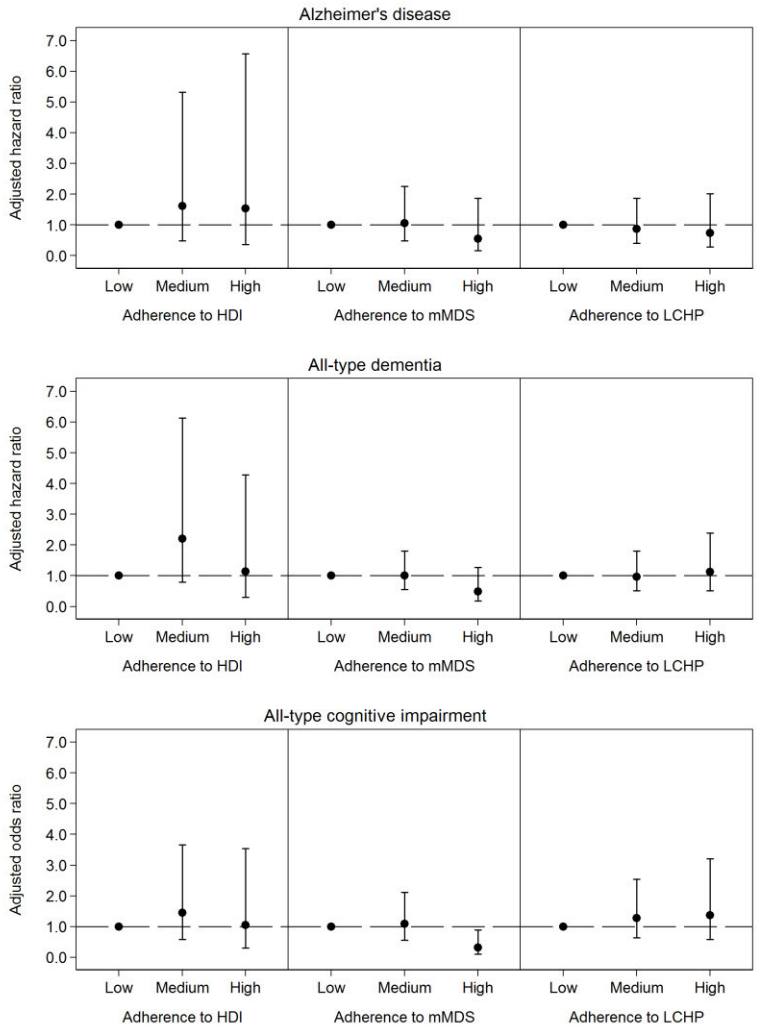

Figure 6. Risk estimates for Alzheimer's disease, All-type dementia, and All-type cognitive impairment in relation to adherence to each diet in the subpopulation. Published in licentiate thesis, 2016.

Paper II

The mean age at baseline was 71 years. Among the 1182 men and during a maximum follow-up of 18 years (median: 12 y and 14,093 person-years at risk), 116 were identified with AD, 64 with vascular dementia, 250 with all-cause dementia, and 80 with cognitive impairment.

The median total vitamin D intake, including vitamin D supplements (n=37), was 5.5 µg/d (range: 4.3–7.1 mg/d). A total of 370 participants had a lower intake than 4.7 µg/d (Figure 7).

The mean (SD) plasma 25(OH)D concentration was 68.7 (19.1) nmol/L. A total of 183 participants had plasma 25(OH)D concentrations <50nmol/L and 20 participants had concentrations <30 nmol/L (Figure 8).

Table 2 shows that a higher genetic risk score (GRS) was associated with higher concentrations of plasma 25(OH)D; 57.5 (18.3) nmol/L for the GRS=0 and 70.9 (22.4) for GRS=4.

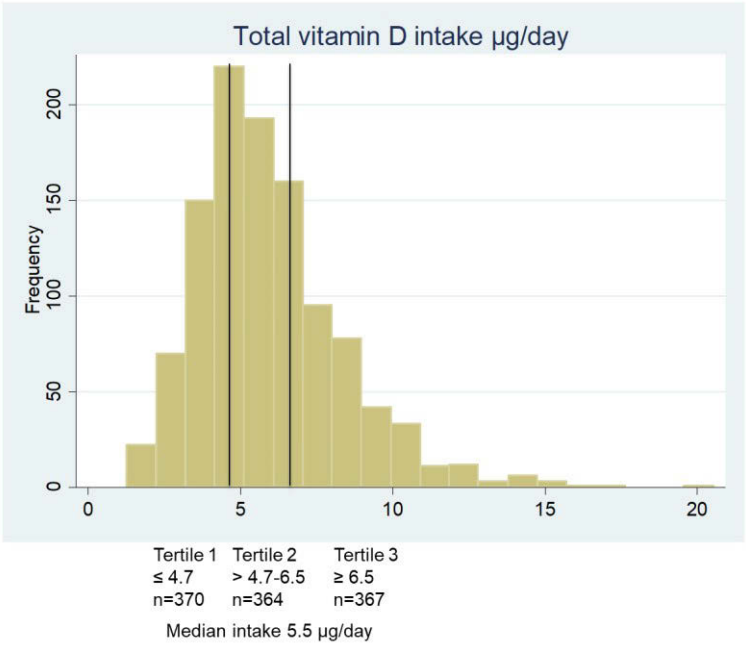

Figure 7. Distribution of total vitamin D intake.
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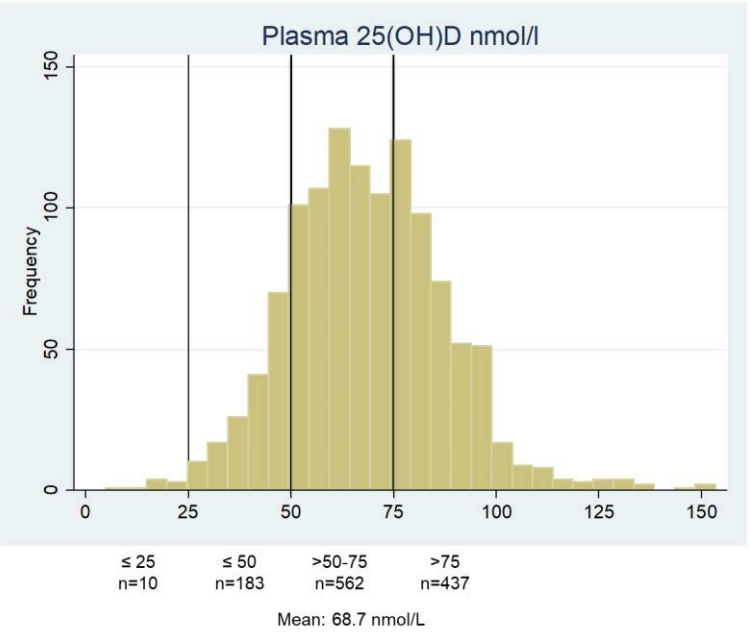


Figure 8. Distribution of 25(OH)D in plasma.
Published in licentiate thesis, 2016.

Table 2. Plasma 25(OH)D by genetic risk score

Genetic risk score	Plasma 25(OH)D nmol/l medel ± SD
0	57.5 ± 18.3
1	67.5 ± 18.1
2	67.6 ± 17.2
3	70.2 ± 19.2
4	70.9 ± 22.4

We observed no associations of dietary vitamin D intake, plasma 25(OH)D, or GRS with AD, vascular dementia, all-cause dementia, or cognitive impairment in any of the analyses, including analysis of potential non-linear associations with adjusted restricted cubic-spline Cox proportional hazards regression analysis (Figure 9 and Figure 10). The adjusted (model 2) HRs for the continuous GRS was 0.96 (95% CI 0.70, 1.18) for AD, 1.08 (95% CI 0.82, 1.42) for vascular dementia, 1.04 (95% CI 0.91, 1.19) for all-cause dementia, and adjusted OR 1.03 (95% CI 0.80, 1.34) for cognitive impairment.

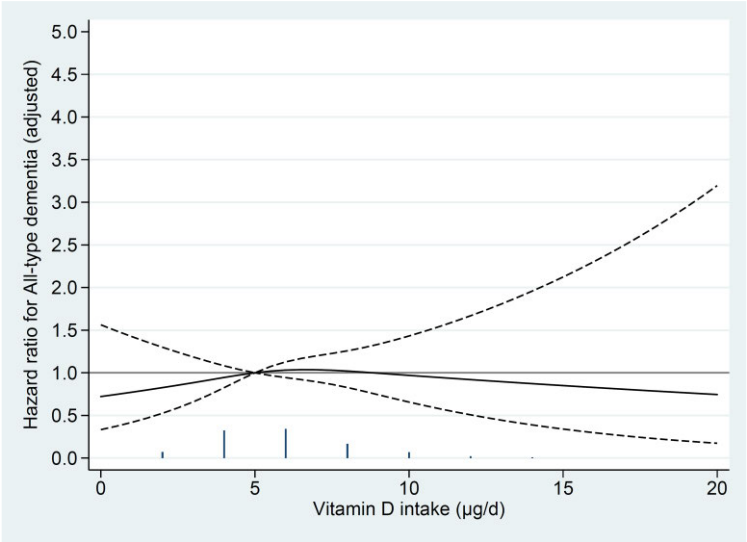


Figure 9. HRs (solid line) and 95% CIs (dotted lines) of all-cause dementia according to total vitamin D intake (n = 1101) including vitamin D from the diet and from vitamin D–containing supplements. Values were estimated with the use of a restricted cubic-spline Cox proportional hazards regression–analysis model with an intake of 5 mg/d as the reference and were adjusted for age, BMI, education, physical activity, energy intake, and smoking. Vertical bars represent the distribution of total vitamin D intake.

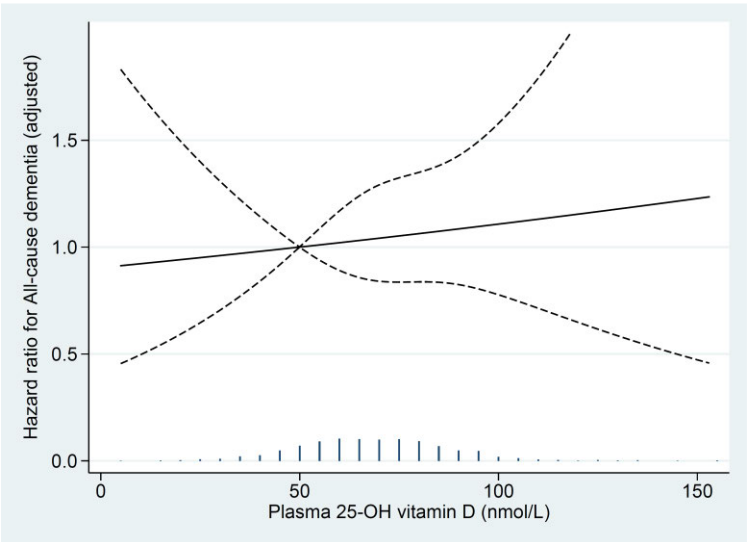


Figure 10. HRs (solid line) and 95% CIs (dotted lines) of all-cause dementia according to plasma 25(OH)D concentrations (n = 1182). Values were estimated with the use of a restricted cubic-spline Cox proportional hazards regression–analysis model with a concentration of 50 nmol/L as the reference and were adjusted for age, season of blood collection, BMI, education, and physical activity. Vertical bars represent the distribution of plasma 25(OH)D.

Paper III

The mean age at baseline was 61 years. Comparing individuals in the highest category of milk consumption to individuals in the lowest category of milk consumption, participants were a little older, more likely to have higher BMI, to have higher total energy intake, lower level of education, to live alone, and to consume less fruit, vegetables and vitamin and mineral supplements. The mean follow-up was 14.9 years (median 17 years and 1,220,072 person years at risk) and during this period 1251 incident cases of PD (475 cases in women and 776 cases in men) were identified among the 81,915 participants. Compared with no or low milk intake (<40 mL/day), HRs for PD were higher among those consuming more milk (HRs 1.14–1.29) and there was no dose-response relationship between milk consumption and risk of PD (Figure 11). No association between fermented milk consumption and incident PD risk was observed.

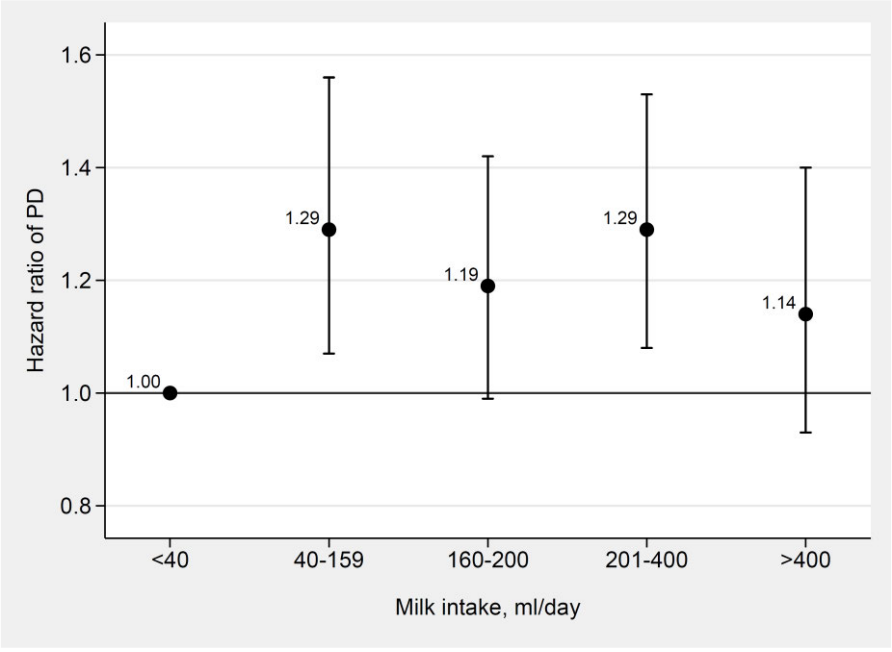


Figure 11. Adjusted hazard ratios for milk intake and incident Parkinson's disease in the whole study population (the Swedish Mammography Cohort and the Cohort of Swedish Men).

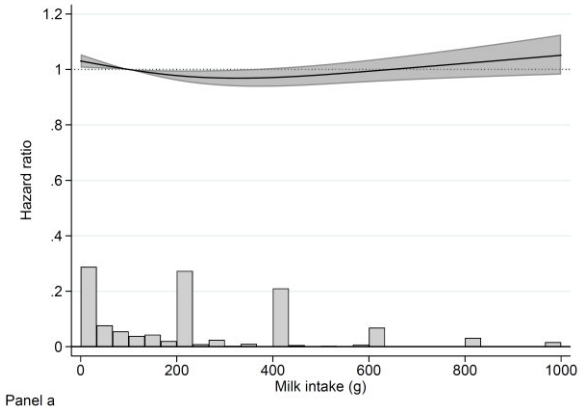
Paper IV

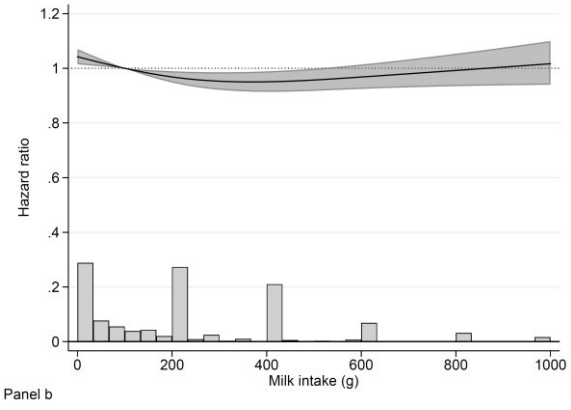
The mean age at baseline was 61.3 years. The mean follow-up was 17.7 years and during this period the consumption of milk intake decreased, and consumption of fermented milk increased among the participants (Table 3). The mean intake per day in 1997 for SMC and COSM was 260 g (281) for milk and 160 g (201) for fermented milk. Participants who consumed less than 200 g/d of milk had, on average, higher alcohol consumption than those who consumed more than 200 g of milk per day. Individuals who had an intake of 600 g of milk per day or more had, on average, greater BMI, higher energy and soft drink intake, lower fruit and vegetable intake, and were less likely to use vitamin- and mineral supplements, lower attained educational level, be current smokers and live alone compared to those who had an intake of less than 600 g of milk per day.

Table 3. Milk and fermented milk intake among participants in The Swedish Mammography Cohort and The Cohort of Swedish Men in 1987, 1997, and 2009.

	1987-1990	1997	2009
	Milk g/day, mean (SD)	Milk g/day, mean (SD)	Milk g/day, mean (SD)
The Swedish Mammography Cohort	244 (202)	230 (248)	213 (251)
The Cohort of Swedish Men		285 (303)	257 (291)
	Fermented milk g/day, mean (SD)	Fermented milk g/day, mean (SD)	Fermented milk g/day, mean (SD)
The Swedish Mammography Cohort	97 (108)	175 (202)	209 (260)
The Cohort of Swedish Men		149 (198)	188 (262)

Among the 79,618 participants, there were 1,407,536 person-years at risk during which 9735 incident cases of total stroke were identified (7573 were cerebral infarctions, 1470 hemorrhagic strokes, and 692 unspecified strokes). No association was observed between time-updated information on milk consumption and risk of total stroke (Figure 12, panel a). A non-linear association was observed between milk consumption and cerebral infarction, such as that milk intake below 100 g/day was associated with a higher risk and intakes between 100-500 g/day were associated with a modestly lower risk but the CIs were wide (Figure 12, panel b). A higher intake of milk was associated with higher risk of hemorrhagic stroke (Figure 12, panel c). No associations were observed between fermented milk consumption and any of the stroke outcomes. Sensitivity analysis including time-updated information from 1987-90 in SMC showed similar results as the main analysis.





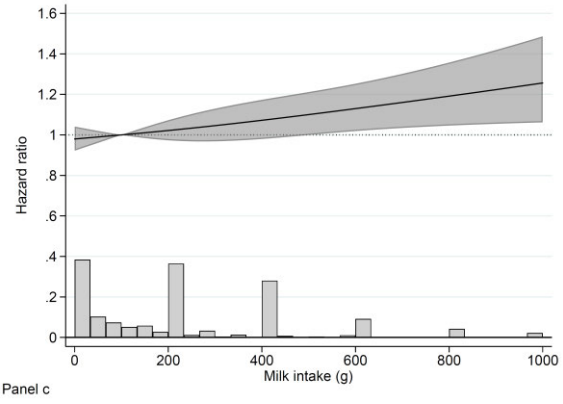


Figure 12. Hazard ratios (solid line) and 95% confidence intervals (gray shaded area) for milk consumption and (panel a) total stroke, (panel b) cerebral infarction, and (panel c) hemorrhagic stroke in The Swedish Mammography Cohort and the Cohort of Swedish Men. 100 g/day was used as reference. The distribution of milk intake is shown in the histogram. Time at risk was accrued between 1 January 1998 and 31 December 2019, with time-updated information in 2009.

Discussion

In these papers we have studied various aspects of diet in relation to cognitive disorders, Parkinson's disease, and stroke in different Swedish populations.

Main findings

No strong associations were found between adherence to dietary patterns and risk of incident dementia and cognitive function. Vitamin D assessed in three different ways, was not associated with incident dementia and cognitive function. Fermented milk consumption was not associated with PD or stroke. Milk consumption was associated with incident PD but not in a dose-dependent manner. There was some evidence of a weak non-linear association with milk consumption and cerebral infarction and a positive association between milk consumption and hemorrhagic stroke.

Main findings in comparison with other studies

Paper I

Numerous studies have investigated associations between healthy dietary patterns and their impact on cognitive function and cognitive decline. Emerging research suggests that healthy dietary patterns (66) preferably plant-based diets and especially the Mediterranean diet protects against, cognitive impairment, cognitive decline, and dementia (75, 177). However, the vast majority of the studies have investigated associations with healthy dietary patterns (mostly adherence to the Mediterranean diet) and cognitive outcomes, while fewer studies have investigated associations between dietary patterns and incident AD and dementia. Our study was among the first to examine the relationship between dietary patterns and dementia diagnosis and cognitive impairment in a northern European population. Focus will now mainly be on AD and dementia because cognitive function has been measured in many ways in studies and it is therefore difficult to compare studies. Moreover, AD and dementia were our main outcomes.

Surprisingly few studies have investigated the association between HDI and AD or dementia (66). We observed no associations between HDI and any

of the outcomes studied, while adherence to HDI was associated with lower risk of AD and dementia in a Finnish study comprised of 385 participants. The follow-up was longer than in our study but with fewer participants (178). Among older American and Europeans a greater adherence to the HDI was not associated with reduced rates of cognitive decline measured with MMSE and modified MMSE (179) while another study observed that adherence to HDI was associated with better cognitive function and slower cognitive decline measured with different tests among middle aged persons in the Netherlands (180).

Contrary to several (70-72, 181-183) but not all (73) studies, we did not find an association between adherence to Mediterranean-like diet and incident AD. Most of the studies where high adherence to the Mediterranean diet was associated with lower risk of AD had a follow-up of less than 5.5 years, which is shorter than the follow-up in our study. Since AD has a long prodromal phase, it is important that the follow-up is not too short to prevent reverse causation.

We did not find an association between adherence to Mediterranean-like diet and all-type dementia, which is in line with other studies. Higher adherence to the Mediterranean diet was not associated with risk for incident dementia in 1410 women and men (mean age of 75.9 years) in France with a mean follow-up of 4.1 years (73). Furthermore, no association was observed between the Mediterranean diet and cognitive impairment or dementia investigated in a cohort of 1220 Australian men and women followed for 12 years (184). Among 28,775 Swedish adults (≥65 years of age) with a mean follow up of 12.6 years and 3755 participants diagnosed with dementia, no association was found between adherence to the Mediterranean diet and risk of dementia (76). No association was found between adherence to the alternate Mediterranean diet score and probable dementia (in elderly American women) (185) or with incident dementia in the Atherosclerosis Risk in Communities (ARIC) Study in the U.S (186). High adherence to a Mediterranean diet, was associated with a lower risk (20%) of overall dementia, in a Spanish cohort, compared to those with low adherence to Mediterranean diet, where the participants were followed for over 20 years (187). However, the authors of the Spanish study pointed out that the protective effect of Mediterranean diet on the risk of dementia was only seen after excluding 30% (n=7204) of the participants who were classified as mis-reporters of energy intake (187). These results are similar to the results in our subpopulation where mis-reporters of energy intake were excluded according to the Goldberg cut off. Exclusion of these participants both in the Spanish and our own cohort might introduce selection bias which will be discussed in the methodological part of the thesis.

Comparison of dietary patterns

The composition of dietary patterns varies between studies which makes it complex to compare studies (188). When using the Mediterranean diet score,

we have to acknowledge that several investigated populations do not have traditionally Mediterranean dietary habits. The scoring of the Mediterranean diet is usually based on the population's median intake of foods and the median serves as the cut-off. Differences in cut-offs for nutrients and foods as well as adjusting for setting of the populations' dietary intake may contribute to differences in results (73, 189). We had to adjust the foods included in the original Mediterranean score to a Swedish dietary setting as described in the method section. A major difference in our population compared to populations around the Mediterranean is the low intake of olive oil, seeds, and nuts, which are key components in the Mediterranean diet. However no association was found in a French cohort with a traditionally high intake of olive oil between Mediterranean diet and dementia (73), while in other populations with a lower consumption of olive than in the Mediterranean found that adherence to Mediterranean diet was associated with lower risk of AD (71).

The WHO recommends whole diet approaches to prevent cognitive decline and dementia (190), and has highlighted the Mediterranean diet as protective but have also stated that prevention of cognitive decline and dementia with the Mediterranean diet is moderate and not harmful (190). The result in our study is in agreement with the statement that adherence to HDI and mMDS is not harmful.

Contrary to Roberts et al who observed a reduced risk of dementia with high percentage of protein intake dementia (191), we found a weak association between high adherence to LCHP and higher risk of incident all cause dementia. Few other studies have investigated the association between LCHP and AD and dementia (52). Volek et al, criticized that low adherers in our population are not really adherent to a low carbohydrate diet since carbohydrates should contribute to less than 30 E% to be defined a low carbohydrate diet (192). High adherers to LCHP in our cohort had a median carbohydrate intake of 42 E% and a median protein intake of 17.5 E% which is not extreme.

Paper II

We observed no associations of vitamin D, measured as vitamin D intake, measured with a 7-day dietary record, plasma concentrations of 25-hydroxyvitamin D (the major clinical biomarker of vitamin D status), or a vitamin D synthesis genetic risk score using Mendelian randomization, with AD, vascular dementia, all-cause dementia, or cognitive impairment. The median reported vitamin D intake was half of the official recommended intake for this age group but despite this, very few participants (15.5%) had low (≤50 nmol/L) plasma 25(OH)D concentrations. Only 10 participants (0.8%) had plasma 25(OH)D concentrations ≤ 25 nmol/L. Exact absolute values of intakes are difficult to establish due to potential misreporting of what is eaten and the exactness with which the food database can capture nutrients in the reported diet. For the plasma vitamin D concentrations, we used the gold

standard method (HPLC-mass spectrometry). In comparison to the gold standard, other methods produce results with lower concentrations (193).

Few prospective observational studies have investigated associations between vitamin D intake and AD and dementia. Unlike the results in our study, a higher vitamin D intake was associated with a lower risk of AD in a study among women in France (93) and a lower risk of dementia in a multiethnic study including both women and men in the US (94). Both these studies had shorter follow-up periods compared to our study and the loss of follow-up was 51.2% in the French study and 21.3% in the US study while there was no loss to follow-up in our study.

Our findings of no association between plasma 25(OH)D and AD or dementia are consistent with studies conducted in Europe (100) and North America (99, 101, 103). However, a large dose response meta-analysis including 10 cohorts (79, 80, 82, 83, 99-102, 194, 195) and 28,640 participants (our study was included) observed a 7% lower risk of AD and 5% lower risk of dementia for every 10 nmol/L increase in 25(OH)D (196). In two other meta-analyses (197, 198), it was shown that only very low concentrations of vitamin D were associated with higher risk of dementia, whereas moderately low levels were not. Of note is that very few participants in our study had vitamin D deficiency.

We observed no associations between the genetic variants involved in the vitamin D synthesis and AD or all-cause dementia. No associations were observed between a combined synthesis score, with the same single nucleotide polymorphisms (SNPs) as in our study, and cognitive performance including 172,349 participants (199). We only included two SNPs as instruments for circulating 25(OH)D with no known pleotropic effects (148, 149). Other MR studies have reported an inverse association between genetically higher 25(OH)D concentrations and AD risk (81, 104, 107, 108). However, the genetic instruments used were different from ours and included four to seven SNPs. These studies included SNPs in the vitamin D binding protein gene which (*GC*), which may have pleotropic effects and is thus not a suitable genetic instrument (148, 200-202). Presence of pleotropic effects violates one of the main assumptions in MR studies (148). In these studies, one of the SNPs (rs12785878 in the gene *DHCR7*) was not significantly associated with AD, neither in our study nor in the other MR studies (81, 104, 107, 108).

So far there is no evidence from randomized controlled trials (RCTs) that vitamin D supplementation would have an impact on cognitive function or risk of dementia (203, 204). RCTs generally have shorter follow-up periods than observational studies, which is a limitation especially regarding the long prodromal phase of dementia, where long follow-up periods are needed.

Dissimilar results between studies may also be due to the fact that very few participants in our study had low concentrations of plasma 25(OH)D. The method for analyzing vitamin D concentrations may differ between studies. An overestimation of the proportion of vitamin D insufficiency analyzed with

DiaSorin chemiluminescence immunoassay compared to HPLC/MS has been observed (193). Further, different methods for ascertainment of dementia may influence the results as discussed below.

Even if we were unable to demonstrate associations between vitamin D and dementia and our study is small, all three ways of measuring vitamin D point in the same direction which is a strength of this study. If different research methods are applied to examine the same research question and show similar results, these are more likely to be robust (205).

Paper III

We found a weak higher risk of PD associated with milk consumption (non-fermented milk) but there was no dose-response relationship, that is, the risk of PD did not increase with increasing milk consumption. Similarly, a recent Mendelian randomization study found that a genetic variant near the *LCT* gene and which is associated with lactase persistence and higher milk (non-fermented) consumption was associated with an increased risk of PD (206). Other observational studies (119-123) also show similar results, although most display a dose-response association. Given the lack of dose-response relationship between milk consumption and PD risk in our study, this association needs to be interpreted with caution and needs further study. Even if already small amounts of milk could influence PD risk, it is also possible that milk drinkers may differ from nondrinkers and low consumers of milk with respect to other risk factors and we cannot exclude influence of residual confounding. We observed no association between fermented milk intake and PD in our Swedish population, which is in line with previous studies (120-122).

Paper IV

We found that a higher long-term milk consumption based on repeated measures of intake was not associated with total stroke, weakly and non-linearly associated with lower risk of cerebral infarction and higher risk of hemorrhagic stroke. Fermented milk consumption was not associated with any stroke type. Our results highlight the importance of repeated measurements of food intake, separate analyses of milk and fermented milk consumption, and to study stroke types separately.

Our results are in line with those from three large European cohorts where no association for milk consumption and total stroke was observed (127-129). By only studying total stroke we may mainly capture associations with cerebral infarction (ischemic stroke), which is the predominant form of stroke (78% of all strokes in our study). Using cerebral infarction as outcome, our findings are also in accordance with results from several other studies and a meta dose response analysis where milk intake was observed to be inversely associated with ischemic stroke (cerebral infarction) (126, 127, 131, 207).

However, other studies observed no association or that a high milk consumption was associated with lower risk of hemorrhagic stroke (127, 133-135), while a higher milk consumption was associated with higher risk of hemorrhagic stroke in our study. Reasons for these discrepant results are unclear and there are only few studies with hemorrhagic stroke as outcome.

A recent MR study found no association between lactase persistence predicted milk intake and risk of total and cerebral infarction (208).

We observed no association between fermented milk intake and cerebral infarction, which is in line with a previous review and meta-analysis (131) but not with a dose response meta-analysis with total and fatal stroke as outcomes that observed nonlinear associations between fermented milk intake and both cerebral infarction and hemorrhagic stroke (135). Differences in results may be due differences in fermented dairy products included in the studies and possibly also due to publication bias (135).

Methodological considerations

Bias

Bias is a weakness or a systematic error in the design, collection, execution, analysis, interpretation, or publication of a study and may result in incorrect associations between exposure and outcome (172). In this section, I will discuss different methodological considerations and biases and how they may have influenced the results.

Study populations

All four papers included in this thesis are based on data from population-based prospective cohort studies with long follow-up time. Participants in the studies were obtained from the general population. Even though we do not have information of those who did not participate in the studies and the participation rate was lower for COSM compared to the participation rate in ULSAM and SMC, all studies are considered to be representative of the general population (139, 209). The men and women who volunteered to participate in the studies might have been healthier than non-participants. For example, one of the original aims in ULSAM was to identify high risk individuals of cardiovascular disease for treatment. Even if participation is non-differential with respect to exposure and outcome, it has been suggested that longitudinal studies with repeat examinations where the healthiest participants are those that return may suffer from selection bias (210). One way to limit this bias is to adjust for factors related to participation (210). In this thesis, covariates selected as confounders are to a large extent also associated with participation and any influence of such bias would therefore be reduced.

In this thesis, the main outcomes were studied with time-to-event analysis. Loss to follow-up can be a problem with long follow-ups and can lead to biased results (172). We had almost no loss to follow-up since all medical journals were reviewed for the participants in ULSAM and outcomes were ascertained though national registers with little or no loss to follow-up for participants in SMC and COSM.

There were very few participants with low concentrations of 25(OH)D in study II, which is in line with previous studies in community-dwelling people (211, 212) in Sweden. Therefore, in the future it would be more relevant to study vitamin D and dementia in another context for instance in a population with low vitamin D status.

Generalizability

Primarily only Caucasians participated in the studies and therefore our results may not apply to other ethnic group with potentially different dietary habits, genetic susceptibility, and prevalence of risk factors. The results in paper II-IV might not apply to other ethnic groups since there are differences in concentrations of plasma 25(OH)D and vitamin D-binding protein and intolerance of milk between ethnic groups (213).

In paper III and IV both women and men were studied but in paper I and II only men were studied, which is a limitation. At the time when ULSAM was initiated cardiovascular disease was common among men and it was considered that mostly men were affected.

All studies included in the thesis were done on middle aged people and the results may therefore not apply to younger people or to children.

Reverse causation

A strength with prospective studies is that the exposure is measured before the outcome which limits revere causation. When studying associations with neurodegenerative diseases, reverse causation needs special attention since the progression of the disease usually starts between 5 to 20 years before the first classical clinical symptoms (5, 214, 215). Early subtle symptoms such as reduced smell (215) and constipation (32, 216) may change dietary intakes. This indicates that the follow-up time should not be too short. All studies included in the thesis had long follow-up of more than 10 years. Also due to ascertainment of diagnoses both by review of medical journals and through registers we could exclude all identified cases before baseline. Repeated measurements including cognitive function was performed before baseline in Paper I and Paper II and thus we might have captured participants with early symptoms. Further, we excluded dementia cases diagnosed within two years of follow-up in paper II and PD cases within the first 3 years of follow-up in paper III (in sensitivity analysis) to limit the risk of reverse causation which we may should have done in paper I as well. In sensitivity analysis in paper IV, we also excluded the first three years of follow up.

Other considerations

ULSAM is a small but well-defined cohort with many of the variables measured. It can be argued that the ULSAM cohort is too small especially for MR studies as in Paper II. However, a causal relationship was found in ULSAM using the MR approach (217), which indicates that if the effect is large enough the causal effect can be detected even in a small study.

In SMC and COSM most variables except those from the registers were self-reported. With self-reporting there is a potential risk of reporting error, as discussed below. However, the use of self-reported questionnaires made it possible to study a large number of people. A large number of people rendered a large number of cases which made it possible to study association with not only incident PD but also cerebral infarction and hemorrhagic stroke, separately. Since the associations between diet and multifactorial disease is probably modest, we needed a large number of participants to detect possible associations.

Measurement of dietary intake

In nutritional epidemiology, we study the impact of diet on health and disease. To measure dietary intake and capture habitual intake is difficult. Most dietary assessment methods rely on self-reported intake with inherited measurement errors. However, all measurements have some form of measurement error and both the method's accuracy and knowledge about the method's limitations is crucial for interpretation of the results.

The intention in our studies was to capture habitual dietary intake. There are however several reasons for misreporting habitual intake. Misreporting of intake is probably not the same for the entire population, some sub-populations under report energy intake to a higher degree than others, further specific foods and meals are misreported to a greater extent than others (218-222). High BMI has been associated with underreporting of energy intake (220, 222, 223).

In Paper I and II, participants recorded their intake for seven consecutive days and the recording itself might have influenced their dietary intake. Also, it can be argued that one week of dietary recording is not enough to capture habitual dietary intake. The FFQ measures habitual intake over a period of time and relies on the participant's memory. Whether the habitual intake is reflected by the FFQ also relies on the number of food items included, whether the food items cover foods specifically related to the research question and whether portion sizes are included. Inaccurate recall of diet and social desirability bias may lead to misclassification of exposure. The desire to report intake in a certain way, maybe due to the norms of society, may also influence the reported intake. At the time of the surveys for SMC and COSM milk and fermented milk were not considered to be healthy or unhealthy foods and there

was probably no reason for under- or overreporting milk and fermented milk intake due to social desirability. Because of the prospective design of the studies and the long follow-up, the misclassification is however unrelated to the outcome and would probably result in attenuated associations.

When we study associations with dietary intake it is implied that the dietary intake is stable during follow-up. In Paper III (in sensitivity analysis for SMC) and Paper IV we had the advantage of repeat measurements and could thus capture potential changes during follow-up which would increase precision and accuracy compared to only one measurement. A limitation in Paper I and II is thus the lack of repeated measurements of dietary intake, vitamin D and plasma 25(OH)D.

Both methods for dietary assessment used in this thesis have been validated and have shown moderate to high agreement with the method it has been validated against (140, 156, 224). The methods have also shown to be reproducible (224). Even though the methods are acceptable there are some more concerns that needs to be mentioned. A validation study for the food record used in ULSAM revealed that the portion sizes may have been too small which resulted in lower reported intakes compared to 24-h recalls (140, 225). This may result in systematic underestimation of energy intake for all participants, but since we are interested in the relative comparison between participants this is of less concern when the full study population is included (140). However, this may also contribute to the large proportion of participants being classified as under reporters, as discussed below.

There will be misreports of dietary intake in all studies and the question is how to further deal with this problem? Extreme reporters of energy intake, as described in the method section, were excluded and dietary variables were adjusted for energy intake to limit misclassification and misreporting (52). We then adjusted for energy intake in the analysis. When adjusting for energy intake the effect of over- and underreporting will be "cancelled" or diminished since nutrients and total energy come from the same foods (52, 226).

In sensitivity analysis in Paper I, we excluded over- and underreporters of energy intake according to the Goldberg method. There are certain assumptions to be addressed. The PAL values that we used in the equation were not measured but arbitrarily chosen and applied on responses from self-reported physical activity estimated with four questions. If the participants systematically overestimated their physical activity due to social desirability, the calculated energy expenditure would be higher than the true energy expenditure and participants would to a higher degree be classified as underreporters of energy intake. What is more problematic, is that we might have introduced bias when stratifying on selection, based on adequate reporters of energy intake according to Goldberg. By excluding half of the population, we might have introduced collider bias. In this case, both exposure and outcome may increase the chances of selection and thus create a "downward" bias which means that we can introduce a negative relationship between exposure and outcome if this

bias is greater than a potential direct relationship (Berkson's bias) (227, 228). This may explain differences in results between the whole population and the subpopulation. For all-type dementia and in comparison to low adherence, the HR for high adherence to mMDS in the whole population was 0.85 and 0.48 in the subpopulation of "adequate reporters". Corresponding HRs for high vs low adherence to the LCHP were 1.59 and 1.12.

Another concern is misclassification of missing information of milk and fermented milk. In the main analyses, missing intake was classified as zero intake. In sensitivity analyses, we excluded those with missing intake and results from the sensitivity analyses did not differ from the main analyses. If the misclassification was random the precision of the association would be attenuated (confidence intervals larger) but if the misclassification was non-random the estimate of the association could be changed in any direction and thus result in spurious results. Fortunately, there was an additional question in the FFQ on whether they consumed milk or not and 92% of those who did not report milk consumption on the FFQ part reported that they did not consume milk when posed this question (153).

The dietary methods used are valid for ranking an individual's intake in relation to others (52). Despite the efforts made, some degree of measurement error in the assessment of dietary intake, vitamin D, milk and fermented milk intake were inevitable, and this may have affected the observed associations.

Measurement of outcome

We had no loss to follow-up. In ULSAM, we captured all participants who got a dementia diagnosis, since all ULSAM participants' medical records were examined. In SMC and COSM, incident cases of PD and stroke were identified by linkage with the Swedish National Patient and Cause of Death Registers (158, 162, 164). Furthermore, case ascertainment did not rely on self-reported information and we therefore had no recall bias. In studies with self-reported diagnosis or in studies with phone interviews there is a possibility of recall bias or loss to follow-up. However, in the patient registers we only capture individuals who have been treated at the hospitals or have seen a specialist. This is of great importance since most patients with dementia are not treated in hospital for these conditions and occurrences of dementia will therefore in most cases be secondary diagnoses. This was not a problem for the diagnosis of dementia and AD in ULSAM (Paper I and II) since we had the individual follow-up of the participants' medical records and could capture all participants who got a dementia diagnosis and not only the ones with severe dementia or comorbidity. This is partly the case also for PD, especially early in the progression of the disease. In the registers we might therefore have captured those with a more severe PD or PD with comorbidity. There is, therefore, a possibility that the association between milk intake and incident PD instead reveals an association with comorbidity or with severe PD instead of incident

PD. With the diagnosis of stroke, we do not have that problem since almost everyone with a potential stroke are referred to the hospital. The potential associations between poor diet and low vitamin D concentrations, as seen in some other studies where only hospital registers were used for identification of cases, might reflect morbidity instead of incident dementia (79, 82, 102).

In the analysis that included MMSE we had a loss to follow-up which may have biased our results. It can be speculated that those who attended the follow-up were healthier than those who did not and the non-participants may have been cognitively impaired. In Paper I, we might have introduced selection bias when creating the diagnosis all-type cognitive impairment because we excluded a significant number of participants where there was no information on cognitive function measured with MMSE. Then, those with all-type dementia was added to cognitive impairment. In the analysis only those with MMSE and all-type dementia were included. Compared to the original cohort this is probably a selected population and not representative for the original population.

Confounding

Confounding, as described by Vandenbroucke et al, "*produces relations that are factually right, but that cannot be interpreted causally because some underlying, unaccounted for factor is associated with both exposure and outcome"* (229). By using DAGs (in Paper II, III, and IV), we tried to find out whether a factor was a confounder that we had to adjust for, whether it was an intermediate or a collider, and whether we introduced bias by adjusting or stratifying for a variable. As mentioned earlier, we might have introduced selection bias by stratifying on reported energy intake. Although we tried to control for confounding there is always the possibility of residual confounding, either by unmeasured confounders or inaccurately measured confounders, since in observational studies, there is no randomization of the participants. In MR studies the confounding is minimized because genetic variants are randomly allocated, as in Paper II where genetic variants for synthesis of vitamin D were used. In Paper IV, we had repeated measurements and we could time-update both exposures and covariates and thus capture possible changes during follow-up.

Clinical implications

In a clinical sense, results from these studies do not imply any changes of the current dietary recommendations concerning dietary patterns, vitamin D, milk, and fermented milk in relation to AD, dementia, cognitive impairment, PD, or stroke. Even though we did not observe that higher adherence to mMDS and HDI were associated with lower risk of dementia, it is not harmful

to recommend a healthy diet. We found a higher risk of hemorrhagic stroke with higher milk intake and somewhat higher risk of dementia with higher adherence to LCHP but further studies are needed to confirm these results.

Concerning vitamin D, there is no association between vitamin D (intake, concentrations or genetic determinants) and dementia among community-dwelling 71-year-old men. Thus, vitamin D supplementation in the general population for decreasing the risk of dementia is not recommended.

Implications for future research

Dietary intake was measured at the age of 70 for participants in the ULSAM study and the mean age in SMC and COSM was 62 years. Concerning the long prodromal phase and the lack of knowledge when the disease is initiated it would be valuable to study dietary intake at a younger age and follow these individuals with repeat measurements. To capture all dementia and PD cases we would need to incorporate the Swedish registers with a national register from the primary care. Today there is no national primary care register that covers the whole of Sweden. Otherwise, we need to identify cases as in ULSAM which would almost be impossible in large cohorts.

The pathophysiology of these diseases is very complex and therefore we need not only to study dietary intake separately but also in combination with other lifestyle factors. A composite score that includes dietary intake, social activity and other lifestyle factors as in the FINGER trial (230) or Chicago Health and Aging Project and the Rush Memory and Aging Project (231) would be valuable. It would also be interesting to study associations with patterns developed for targeting diseases in the brain as the Mediterranean-DASH Diet Intervention for Neurodegenerative Delay diet but adapted to our dietary habits as the Nordic diet. Also combining dietary intake, with objective measurements of dietary intake, and MR studies is needed.

Summary and conclusions

In this thesis we have studied various aspects of diet in relation to cognitive disorders, Parkinson's disease, and stroke in different Swedish populations. No strong associations were found between adherence to dietary patterns and risk of incident dementia and cognitive function. Vitamin D assessed in three different ways was not associated with incident dementia and cognitive function. Milk consumption did not seem to have an important impact on the development of PD. Fermented milk consumption was not associated with PD or stroke. Nevertheless, there was some evidence of a weak non-linear inverse association between milk consumption and cerebral infarction, but a positive association between milk consumption and hemorrhagic stroke.

Paper I was one of the first studies that investigated dietary patterns in relation to cognitive impairment in a population from Northern Europe. It was also, to the best of my knowledge, the first to study adherence to the Low Carbohydrate High Protein score diet in relation to cognitive impairment and dementia. Paper II was the first study to examine vitamin D in three different aspects and the impact on dementia. Of note is that we had complete and valid ascertainment of dementia diagnosis in all participants in both Paper I and Paper II, which reduces misclassification of the outcome and potential bias. In Paper III and IV, we investigated the effect of milk and fermented milk consumption separately on the risk of PD and stroke (total and subtypes) in a large cohort study that included both women and men with a wide range of both milk and fermented milk intake. In Paper IV, we had repeated measurements of dietary intake, which allowed us to time-update information on exposures and covariates and thus capture diet and lifestyle changes and to improve precision and accuracy of the observed associations. We found that milk and fermented milk consumption had different impacts on cerebral infarction and hemorrhagic stroke, which demonstrates the importance of investigating different milk products and different stroke types separately.

In summary, no strong associations were found between the investigated aspects of diet and common disorders and diseases in the brain. Our results do not however indicate that it is harmful for cognitive disorders, PD, or stroke to adhere do the official dietary recommendations which prevents many other diseases such as diabetes and cardiovascular diseases. Despite the lack of strong associations, the findings of this thesis have increased our knowledge about the potential role of overall diet, vitamin D, and milk and fermented

milk consumption in the prevention or development of common neurodegenerative diseases and stroke.

Sammanfattning - Summary in Swedish

Demens, Parkinsons sjukdom (PD) och stroke är vanliga neurologiska sjukdomar eller störningar som drabbar många människor. Även om riskfaktorer för demens, PD och stroke har studerats i stor utsträckning finns det fortfarande forskningsluckor om kostens roll för utvecklingen av dessa sjukdomar. Idag finns det symtomlindrande läkemedel men fortfarande inget botemedel mot vare sig Alzheimers sjukdom (AD), den vanligaste formen av demens, eller PD. Därför är det viktigt att identifiera förändringsbara riskfaktorer, såsom kost, som påverkar risken för dessa sjukdomar. I min avhandling har jag studerat om olika dieter och D-vitamin kan spela en roll för att förebygga demens och kognitiv försämring och om konsumtion av mjölk och fermenterad mjölk påverkar risken att utveckla Parkinsons sjukdom och stroke hos svenska medelålders och äldre kvinnor och män.

De två första studierna är baserade på data från Uppsala Longitudinal Study of Adult Men (ULSAM). Under perioden 1970–73 inbjöds alla män, födda 1920–24 och bosatta i Uppsala län, att delta i en hälsoundersökning i vilken 2322 av de 2841 inbjudna männen deltog. Deltagarna har därefter undersökts regelbundet och den tredje undersökningen som genomfördes 1991–95, när deltagarna var 71 år, är startdatum för studie I och II. Förutom mätningar av kroppsstorlek, blodprovstagning, minnestestning och hälsoenkäter, ingick även en kostundersökning.

Studie III och IV är baserade på data från två befolkningsstudier, the Swedish Mammography Cohort (SMC) och Cohort of Swedish Men (COSM). SMC-kohorten startade åren 1987–90 då alla kvinnor födda 1914–1948 och bosatta i Västmanlands och Uppsala län blev inbjudna att delta i en studie i samband med en kallelse till den första omgången av mammografiscreening. Totalt bjöds 90 303 kvinnor in varav 66 651 (74 %) svarade på det första frågeformuläret. Enkäten inkluderade frågor om kost och matvanor, civilstånd, utbildning, vikt, längd och bröstcancer. Enkätundersökningen upprepades sedan 1997 och 2008/2009 och då ingick även frågor om bland annat fysisk aktivitet och rökning. COSM startades 1997 och består av män, födda 1918–1952 och bosatta i Västmanlands och Örebro län. Samma livsstilsformulär som skickades ut till kvinnorna i SMC 1997 skickades ut till 100 303 män och 49 % svarade (n=48,850) på enkäten. Undersökningen upprepades 2008/2009.

I ULSAM registrerade 1138 av 1221 (73 %) deltagare sitt matintag, i en förkodad matdagbok, under sju dagar. I SMC och COSM fick deltagarna svara

på om hur ofta de ätit och druckit olika livsmedel under det senaste halvåret. Här användes ett livsmedelsfrekvensformulär (FFQ) för att undersöka matvanorna. För att identifiera demensdiagnos har samtliga ULSAM-deltagares journaler från Akademiska sjukhuset i Uppsala, primärvård och äldreboenden granskats. Information om Parkinsons sjukdom och stroke inhämtades från Patient- och dödsorsaksregistret.

I delarbete I undersökte vi hur tre olika kostmönster relaterar till utvecklingen av demens, inklusive AD, och kognitiv försämring (demens + försämring på kognitivt test) bland deltagarna i ULSAM. Vi följde deltagarna i 12 år och under denna period utvecklade 85 av deltagarna Alzheimers sjukdom (AD), 143 demenssjukdom (inklusive AD) och 198 kognitiv försämring (här ingår de med demenssjukdom och de som har en kognitiv försämring men inte fått en demensdiagnos). Vi observerade inga samband mellan Healthy Diet Indicator (hälsosamt kostmönster rekommenderat av världshälsoorganisationen, WHO) eller en modifierad Medelhavslik kost och insjuknandet i demenssjukdom eller försämring av kognitiv funktion. Däremot fann vi en svag tendens till att hög följsamhet till en diet karaktäriserad av lågt kolhydrat- och högt proteinintag ökade risken att insjukna i demens. Sammanfattningsvis observerade vi inga starka samband mellan kostmönster och insjuknande i demenssjukdom.

I studie II undersökte vi om Vitamin D mätt på tre olika sätt relaterar till demenssjukdom, inklusive AD, vaskulär demens och kognitiv försämring (mätt med Mini Mental Test) bland deltagarna i ULSAM. Vi följde deltagarna i 18 år och under denna period utvecklade 116 deltagare AD, 64 deltagare vaskulär demens, 250 deltagare demenssjukdom (inklusive AD och vaskulär demens) och 80 deltagare kognitiv försämring mätt med ett minnestest. Vi observerade inga samband mellan vitamin D intag, plasma 25(OH)D (markör för vitamin D-status) eller genetiskt risk score (gener involverade i vitamin D-syntesen) och demenssjukdom eller kognitiv försämring.

I studie III studerade vi mjölk- och filmjölkskonsumtion (inklusive yoghurt) i relation till risk för Parkinsons sjukdom i SMC och COSM. Av de 81 915 deltagarna utvecklade 1251 PD under uppföljningen (genomsnittlig uppföljningstid 14,9 år). Mjölkintag ökade risken något för insjuknande i PD i jämförelse med de som inte drack mjölk. Dock såg vi inget dos-responssambad vilket innebär att risken inte ökade med ökande intag av mjölk. Detta resultat måste därför tolkas med försiktighet. Intag av fil- och yoghurt var inte relaterat till PD.

I studie IV undersökte vi mjölk- och filmjölkskonsumtion (inklusive yoghurt) i relation till insjuknande i stroke i SMC och COSM. I denna studie använde vi oss av information från de upprepade mätningarna och kunde tidsuppdatera data i analyser och på så sätt ta hänsyn till eventuella kostförändringar under uppföljningen. Vi följde i genomsnitt de 79 618 deltagarna i 17,7 år och 9735 av deltagarna diagnostiserades med stroke, varav 7573 med cere-

bral infarkt och 1470 med hjärnblödning. Vi fann inga samband med mjölkkonsumtion och stroke men vi fann ett svagt icke linjärt samband mellan ökat mjölkintag och lägre risk för cerebral infarkt. Däremot ökade risken något för hjärnblödning med ökat intag av mjölk. Intag av filmjölk och yoghurt var inte relaterat till stroke, cerebral infarkt eller hjärnblödning. Resultaten understryker vikten av att studera dessa två stroketyper separat och inte som totalstroke samt att också undersöka mjölk och filmjölk separat och inte som totalt intag av mjölkprodukter.

Vi fann inga starka samband mellan olika dieter och uppkomst av demenssjukdom eller kognitiv förändring. Även om vi våra resultat tyder på att kosten inte tycks ha en betydande roll i prevention av kognitiv svikt och demens så visar resultaten inte på att det skulle vara skadligt att följa de allmänna kostråden som förebygger andra livsstilsrelaterade sjukdomar. Vitamin D mätt på tre olika sätt var inte relaterat till demenssjukdom eller kognitiv förändring. Intag av mjölk verkar inte ha någon större påverkan för uppkomst av PD. Vi fann inga samband mellan fil- och yoghurtkonsumtion och PD. Intag av mjölk minskade risken för cerebral infarkt men sambandet var icke linjärt och svagt. Däremot såg vi att ett ökat intag av mjölk ökade risken något för hjärnblödning. Trots att vi inte fann några starka samband har resultaten i denna avhandling ökat vår kunskap om kostens betydelse för prevention av sjukdomar i hjärnan.

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References

1. World Health Organization. Global status report on the public health response to dementia. Licence: CC BY-NC-SA 3.0 IGO. Geneva, 2021.
2. Socialstyrelsen. Nationella riktlinjer – Utvärdering 2018. Vård och omsorg vid demenssjukdom 2018. Indikatorer och underlag för bedömningar. Socialstyrelsen, 2018,
3. Fratiglioni L, et al. Demensförekomst i Sverige: geografiska och tidsmässiga trender 2001-2013. Resultat från den svenska nationella studien om åldrande,
4. Patterson C. World Alzheimer report 2018. London.
5. Bateman RJ, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *New England Journal of Medicine* 2012;367(9):795-804.
6. Dubois B, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement* 2016;12(3):292-323.
7. Small BJ, et al. Cognitive deficits in preclinical Alzheimer's disease. *Acta Neurologica Scandinavica Supplementum* 2003;179:29-33.
8. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement* 2021;17(3):327-406.
9. Blennow K, et al. Alzheimer's disease. *Lancet* 2006;368(9533):387-403.
10. Hardy J, et al. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002;297(5580):353-356.
11. Hardy J, et al. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends in Pharmacological Sciences* 1991;12(10):383-388.
12. Sahathevan R, et al. Dementia, stroke, and vascular risk factors; a review. *International Journal of Stroke* 2012;7(1):61-73.
13. Neary D, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;51(6):1546-1554.
14. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. *Journal of Alzheimer's Disease* 2006;9(3 Suppl):417-423.
15. Kawas CH, et al. Multiple pathologies are common and related to dementia in the oldest-old: The 90+ Study. *Neurology* 2015;85(6):535-542.
16. Sheehan B. Assessment scales in dementia. *Therapeutic Advances in Neurological Disorders* 2012;5(6):349-358.
17. Folstein MF, et al. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12(3):189-198.
18. Weintraub S, et al. Measuring cognition and function in the preclinical stage of Alzheimer's disease. *Alzheimers Dement (N Y)* 2018;4:64-75.
19. Samieri C, et al. Association of Cardiovascular Health Level in Older Age With Cognitive Decline and Incident Dementia. *JAMA* 2018;320(7):657-664.
20. Livingston G, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;396(10248):413-446.

21. Parkinson J. *An Essay on the Shaking Palsy*. London, UK: Whittingham and Rowland for Sherwood, Needly and Jones; 1817.
22. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurology* 2018;17(11):939-953.
23. Gustavsson A, et al. Cost of disorders of the brain in Europe 2010. *European Neuropsychopharmacology* 2011;21(10):718-779.
24. de Lau LM, et al. Epidemiology of Parkinson's disease. *Lancet Neurology* 2006;5(6):525-535.
25. Hirsch L, et al. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. *Neuroepidemiology* 2016;46(4):292-300.
26. Rodriguez-Oroz MC, et al. Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. *Lancet Neurology* 2009;8(12):1128-1139.
27. Fahn S, et al. Neurodegeneration and neuroprotection in Parkinson disease. *NeuroRx* 2004;1(1):139-154.
28. Surmeier DJ, et al. The pathology roadmap in Parkinson disease. *Prion* 2013;7(1):85-91.
29. Connolly BS, et al. Pharmacological treatment of Parkinson disease: a review. *JAMA* 2014;311(16):1670-1683.
30. Obeso JA, et al. Missing pieces in the Parkinson's disease puzzle. *Nature Medicine* 2010;16(6):653-661.
31. Kouli A, et al. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In: Stoker TB, Greenland JC, eds. *Parkinson's Disease: Pathogenesis and Clinical Aspects*. Brisbane (AU): Codon Publications, 2018.
32. Armstrong MJ, et al. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA* 2020;323(6):548-560.
33. Hirsch EC, et al. Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurology* 2009;8(4):382-397.
34. Puspita L, et al. Oxidative stress and cellular pathologies in Parkinson's disease. *Molecular Brain* 2017;10(1):1-12.
35. Blesa J, et al. Oxidative stress and Parkinson's disease. *Frontiers in Neuroanatomy* 2015;9:1-9.
36. Dzamko N, et al. Inflammation is genetically implicated in Parkinson's disease. *Neuroscience* 2015;302:89-102.
37. Kalia LV, et al. Parkinson's disease. *Lancet (London, England)* 2015;386(9996):896-912.
38. Fuzzati-Armentero MT, et al. Peripheral-Central Neuroimmune Crosstalk in Parkinson's Disease: What Do Patients and Animal Models Tell Us? *Frontiers in Neurology* 2019;10:232.
39. Hill AE, et al. What Is Our Understanding of the Influence of Gut Microbiota on the Pathophysiology of Parkinson's Disease? *Frontiers in Neuroscience* 2021;15:708587.
40. Lindsay MP, et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2019. *International Journal of Stroke* 2019;14(8):806-817.
41. Feigin VL, et al. Global Burden of Stroke. *Circulation Research* 2017;120(3):439-448.
42. Socialstyrelsen. Statistics on Stroke 2019. Art no. 2020-11-7048. 2020. (https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2020-11-7048.pdf). (Accessed September 27, 2021).
43. Aho K, et al. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bulletin of the World Health Organization* 1980;58(1):113-130.

44. Virani SS, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation* 2021;143(8):e254-e743.
45. Morais Filho AB, et al. The physiopathology of spontaneous hemorrhagic stroke: a systematic review. *Reviews in the Neurosciences* 2021;32(6):631-658.
46. Sacco RL, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44(7):2064-2089.
47. Algurén B, et al. Functioning of stroke survivors--A validation of the ICF core set for stroke in Sweden. *Disability and Rehabilitation* 2010;32(7):551-559.
48. O'Donnell MJ, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016;388(10046):761-775.
49. Larsson SC. Dietary Approaches for Stroke Prevention. *Stroke* 2017;48(10):2905-2911.
50. Melzer TM, et al. In Pursuit of Healthy Aging: Effects of Nutrition on Brain Function. *International Journal of Molecular Sciences* 2021;22(9).
51. Hartman AM, et al. Variability in nutrient and food intakes among older middle-aged men. Implications for design of epidemiologic and validation studies using food recording. *American Journal of Epidemiology* 1990;132(5):999-1012.
52. Willett W. *Nutritional Epidemiology 3rd Ed*. 2 nd ed. New York: Oxford University Press; 2013.
53. Schulz CA, et al. Advances in dietary pattern analysis in nutritional epidemiology. *European Journal of Nutrition* 2021.
54. Cena H, et al. Defining a Healthy Diet: Evidence for The Role of Contemporary Dietary Patterns in Health and Disease. *Nutrients* 2020;12(2).
55. Huijbregts P, et al. Dietary pattern and 20 year mortality in elderly men in Finland, Italy, and The Netherlands: longitudinal cohort study. *BMJ* 1997;315(7099):13-17.
56. van de Rest O, et al. Dietary patterns, cognitive decline, and dementia. *Advances in Nutrition* 2015;6(2):154-168.
57. Trichopoulou A, et al. Adherence to a Mediterranean diet and survival in a Greek population. *New England Journal of Medicine* 2003;348(26):2599-2608.
58. Hession M, et al. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obesity Reviews* 2009;10(1):36-50.
59. Astrup A, et al. Atkins and other low-carbohydrate diets: hoax or an effective tool for weight loss? *Lancet* 2004;364(9437):897-899.
60. Noto H, et al. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. *PloS One* 2013;8(1):e55030.
61. Johansson I, et al. Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden. *Nutrition Journal* 2012;11:40.
62. Sjogren P, et al. Mediterranean and carbohydrate-restricted diets and mortality among elderly men: a cohort study in Sweden. *American Journal of Clinical Nutrition* 2010;92(4):967-974.
63. Lagiou P, et al. Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. *Journal of Internal Medicine* 2007;261(4):366-374.
64. Michaelsson K, et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ* 2014;349:g6015.

65. van den Brink AC, et al. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diets Are Associated with Less Cognitive Decline and a Lower Risk of Alzheimer's Disease-A Review. *Advances in Nutrition* 2019;10(6):1040-1065.
66. Liu YH, et al. Dietary Pattern, Diet Quality, and Dementia: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Journal of Alzheimer's Disease* 2020;78(1):151-168.
67. Akbaraly TN, et al. Association of Midlife Diet With Subsequent Risk for Dementia. *JAMA* 2019;321(10):957-968.
68. Abell JG, et al. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. *European Heart Journal* 2018;39(33):3119-3125.
69. Radd-Vagenas S, et al. Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. *American Journal of Clinical Nutrition* 2018;107(3):389-404.
70. Gu Y, et al. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. *Journal of Alzheimer's Disease* 2010;22(2):483-492.
71. Scarmeas N, et al. Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology* 2006;59(6):912-921.
72. Scarmeas N, et al. Physical activity, diet, and risk of Alzheimer disease. *JAMA* 2009;302(6):627-637.
73. Féart C, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. *JAMA* 2009;302(6):638-648.
74. Roberts RO, et al. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders* 2010;29(5):413-423.
75. Chen X, et al. Dietary Patterns and Cognitive Health in Older Adults: A Systematic Review. *Journal of Alzheimer's Disease* 2019;67(2):583-619.
76. Larsson SC, et al. The Role of Lifestyle Factors and Sleep Duration for Late-Onset Dementia: A Cohort Study. *Journal of Alzheimer's Disease* 2018;66(2):579-586.
77. Sindi S, et al. Healthy Dietary Changes in Midlife Are Associated with Reduced Dementia Risk Later in Life. *Nutrients* 2018;10(11).
78. Anjum I, et al. The Role of Vitamin D in Brain Health: A Mini Literature Review. *Cureus* 2018;10(7):e2960.
79. Afzal S, et al. Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia. *Alzheimers Dement* 2014;10(3):296-302.
80. Licher S, et al. Vitamin D and the Risk of Dementia: The Rotterdam Study. *Journal of Alzheimer's Disease* 2017;60(3):989-997.
81. Larsson SC, et al. Serum Parathyroid Hormone, 25-Hydroxyvitamin D, and Risk of Alzheimer's Disease: A Mendelian Randomization Study. *Nutrients* 2018;10(9).
82. Littlejohns TJ, et al. Vitamin D and the risk of dementia and Alzheimer disease. *Neurology* 2014;83(10):920-928.
83. Feart C, et al. Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. *Alzheimers Dement* 2017;13(11):1207-1216.
84. Chai B, et al. Vitamin D deficiency as a risk factor for dementia and Alzheimer's disease: an updated meta-analysis. *BMC Neurology* 2019;19(1):284.
85. Perez-Lopez FR, et al. Vitamin D and aging: beyond calcium and bone metabolism. *Maturitas* 2011;69(1):27-36.

86. Amer M, et al. Relation between serum 25-hydroxyvitamin D and C-reactive protein in asymptomatic adults (from the continuous National Health and Nutrition Examination Survey 2001 to 2006). *American Journal of Cardiology* 2012;109(2):226-230.
87. Aspell N, et al. Is there a role for vitamin D in supporting cognitive function as we age? *Proceedings of the Nutrition Society* 2018;77(2):124-134.
88. Mizwicki MT, et al. Genomic and nongenomic signaling induced by 1alpha,25(OH)2-vitamin D3 promotes the recovery of amyloid-beta phagocytosis by Alzheimer's disease macrophages. *Journal of Alzheimer's Disease* 2012;29(1):51-62.
89. Dursun E, et al. A novel perspective for Alzheimer's disease: vitamin D receptor suppression by amyloid-beta and preventing the amyloid-beta induced alterations by vitamin D in cortical neurons. *Journal of Alzheimer's Disease* 2011;23(2):207-219.
90. Holick MF. Sunlight, UV Radiation, Vitamin D, and Skin Cancer: How Much Sunlight Do We Need? *Advances in Experimental Medicine and Biology* 2020;1268:19-36.
91. Annweiler C, et al. Vitamin D and ageing: neurological issues. *Neuropsychobiology* 2010;62(3):139-150.
92. Buell JS, et al. Vitamin D and neurocognitive dysfunction: preventing "D"ecline? *Molecular Aspects of Medicine* 2008;29(6):415-422.
93. Annweiler C, et al. Higher vitamin D dietary intake is associated with lower risk of alzheimer's disease: a 7-year follow-up. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2012;67(11):1205-1211.
94. Zhao C, et al. Vitamin D intake is associated with dementia risk in the Washington Heights-Inwood Columbia Aging Project (WHICAP). *Alzheimers Dement* 2020;16(10):1393-1401.
95. Annweiler C, et al. Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. *Journal of Alzheimer's Disease* 2013;33(3):659-674.
96. Annweiler C, et al. Meta-Analysis of Memory and Executive Dysfunctions in Relation to Vitamin D. *Journal of Alzheimer's Disease* 2013;37(1):147-171.
97. van der Schaft J, et al. The association between vitamin D and cognition: A systematic review. *Ageing Res Rev* 2013.
98. Buell JS, et al. 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. *Neurology* 2010;74(1):18-26.
99. Karakis I, et al. Association of Serum Vitamin D with the Risk of Incident Dementia and Subclinical Indices of Brain Aging: The Framingham Heart Study. *Journal of Alzheimer's Disease* 2016;51(2):451-461.
100. Graf CE, et al. Vitamin D is not associated with cognitive status in a cohort of very old hospitalized patients. *Journal of Alzheimer's Disease* 2014;42 Suppl 3:S53-61.
101. Schneider AL, et al. Vitamin D and cognitive function and dementia risk in a biracial cohort: the ARIC Brain MRI Study. *European Journal of Neurology* 2014;21(9):1211-1218, e1269-1270.
102. Knekt P, et al. Serum 25-hydroxyvitamin d concentration and risk of dementia. *Epidemiology* 2014;25(6):799-804.
103. Duchaine CS, et al. Vitamin D status, cognitive decline and incident dementia: the Canadian Study of Health and Aging. *Canadian Journal of Public Health Revue Canadienne de Santé Publique* 2020;111(3):312-321.
104. Mokry LE, et al. Genetically decreased vitamin D and risk of Alzheimer disease. *Neurology* 2016;87(24):2567-2574.

105. Jorde R, et al. Vitamin D and cognitive function: The Tromso Study. *Journal of the Neurological Sciences* 2015;355(1-2):155-161.
106. Alfred T, et al. Genetic variants influencing biomarkers of nutrition are not associated with cognitive capability in middle-aged and older adults. *Journal of Nutrition* 2013;143(5):606-612.
107. Larsson SC, et al. Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ* 2017;359:j5375.
108. Wang L, et al. Circulating Vitamin D Levels and Alzheimer's Disease: A Mendelian Randomization Study in the IGAP and UK Biobank. *Journal of Alzheimer's Disease* 2020;73(2):609-618.
109. Burgess S, et al. Interpreting findings from Mendelian randomization using the MR-Egger method. *European Journal of Epidemiology* 2017;32(5):377-389.
110. Didelez V, et al. Mendelian randomization as an instrumental variable approach to causal inference. *Statistical Methods in Medical Research* 2007;16(4):309-330.
111. Davies NM, et al. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* 2018;362:k601.
112. Brondum-Jacobsen P, et al. No evidence that genetically reduced 25-hydroxyvitamin D is associated with increased risk of ischaemic heart disease or myocardial infarction: a Mendelian randomization study. *International Journal of Epidemiology* 2015;44(2):651-661.
113. Goodwill AM, et al. A Systematic Review and Meta-Analysis of The Effect of Low Vitamin D on Cognition. *Journal of the American Geriatrics Society* 2017;65(10):2161-2168.
114. Rossom RC, et al. Calcium and vitamin D supplementation and cognitive impairment in the women's health initiative. *Journal of the American Geriatrics Society* 2012;60(12):2197-2205.
115. Manders M, et al. The effect of a nutrient dense drink on mental and physical function in institutionalized elderly people. *The Journal of Nutrition, Health & Aging* 2009;13(9):760-767.
116. Stein MS, et al. A randomized controlled trial of high-dose vitamin D2 followed by intranasal insulin in Alzheimer's disease. *Journal of Alzheimer's Disease* 2011;26(3):477-484.
117. Beauchet O, et al. Effects of Vitamin D and Calcium Fortified Yogurts on Gait, Cognitive Performances, and Serum 25-Hydroxyvitamin D Concentrations in Older Community-Dwelling Females: Results from the GAit, MEmory, Dietary and Vitamin D (GAME-D2) Randomized Controlled Trial. *Nutrients* 2019;11(12).
118. Boulos C, et al. Nutritional Risk Factors, Microbiota and Parkinson's Disease: What Is the Current Evidence? *Nutrients* 2019;11(8).
119. Park M, et al. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. *Neurology* 2005;64(6):1047-1051.
120. Chen H, et al. Consumption of dairy products and risk of Parkinson's disease. *American Journal of Epidemiology* 2007;165(9):998-1006.
121. Saaksjarvi K, et al. A cohort study on diet and the risk of Parkinson's disease: the role of food groups and diet quality. *British Journal of Nutrition* 2013;109(2):329-337.
122. Kyrozis A, et al. Dietary and lifestyle variables in relation to incidence of Parkinson's disease in Greece. *European Journal of Epidemiology* 2013;28(1):67-77.
123. Hughes KC, et al. Intake of dairy foods and risk of Parkinson disease. *Neurology* 2017;89(1):46-52.

124. Zhang X, et al. Milk consumption and multiple health outcomes: umbrella review of systematic reviews and meta-analyses in humans. *Nutrition & Metabolism* 2021;18(1):7.
125. Willett WC, et al. Milk and Health. *New England Journal of Medicine* 2020;382(7):644-654.
126. Soedamah-Muthu SS, et al. Dairy Consumption and Cardiometabolic Diseases: Systematic Review and Updated Meta-Analyses of Prospective Cohort Studies. *Curr Nutr Rep* 2018;7(4):171-182.
127. Tong TYN, et al. The associations of major foods and fibre with risks of ischaemic and haemorrhagic stroke: a prospective study of 418 329 participants in the EPIC cohort across nine European countries. *European Heart Journal* 2020;41(28):2632-2640.
128. Johansson I, et al. Dairy Product Intake and Cardiometabolic Diseases in Northern Sweden: A 33-Year Prospective Cohort Study. *Nutrients* 2019;11(2).
129. Sonestedt E, et al. Dairy products and its association with incidence of cardiovascular disease: the Malmo diet and cancer cohort. *European Journal of Epidemiology* 2011;26(8):609-618.
130. Fontecha J, et al. Milk and Dairy Product Consumption and Cardiovascular Diseases: An Overview of Systematic Reviews and Meta-Analyses. *Advances in Nutrition* 2019;10(suppl_2):S164-S189.
131. Jakobsen MU, et al. Intake of dairy products and associations with major atherosclerotic cardiovascular diseases: a systematic review and meta-analysis of cohort studies. *Scientific Reports* 2021;11(1):1303.
132. Elwood PC, et al. Milk consumption, stroke, and heart attack risk: evidence from the Caerphilly cohort of older men. *Journal of Epidemiology and Community Health* 2005;59(6):502-505.
133. Larsson SC, et al. Dairy foods and risk of stroke. *Epidemiology* 2009;20(3):355-360.
134. Kinjo Y, et al. Possible protective effect of milk, meat and fish for cerebrovascular disease mortality in Japan. *Journal of Epidemiology* 1999;9(4):268-274.
135. de Goede J, et al. Dairy Consumption and Risk of Stroke: A Systematic Review and Updated Dose-Response Meta-Analysis of Prospective Cohort Studies. *J Am Heart Assoc* 2016;5(5).
136. Larsson SC, et al. Dairy consumption and risk of stroke in Swedish women and men. *Stroke* 2012;43(7):1775-1780.
137. Zethelius B, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *New England Journal of Medicine* 2008;358(20):2107-2116.
138. Byberg L, et al. Total mortality after changes in leisure time physical activity in 50 year old men: 35 year follow-up of population based cohort. *BMJ* 2009;338:b688.
139. Harris H HN, Olofsson C, Stackelberg O, Julin B, Åkesson A, et al. . The Swedish mammography cohort and the cohort of Swedish men: study design and characteristics of two population-based longitudinal cohorts. OA Epidemiology 2013 Oct 01;1(2):16. *OA Epidemiology* 2013.
140. Nydahl M, et al. Comparison between optical readable and open-ended weighed food records. *Food & Nutrition Research* 2009;53:Epub DOI 10.3402/fnr.v3453i3400.1889.
141. Becker W. Food habits and intake in Sweden 1989 (in Swedish). *Uppsala: The Swedish National Food Administration; 1994*.
142. Nordin M. MA Ts. Nutrient calculation system designed for research and education. *Västerås: Rudans Lättdata* 1994.

143. WHO. Diet, nutrition and the prevention of chronic diseases. *World Health Organization Technical Report Series* 2003;916:i-viii, 1-149, backcover.
144. Trichopoulou A, et al. Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. *European Journal of Clinical Nutrition* 2007;61(5):575-581.
145. Hollis BW. Measuring 25-hydroxyvitamin D in a clinical environment: challenges and needs. *American Journal of Clinical Nutrition* 2008;88(2):507S-510S.
146. Melhus H, et al. Plasma 25-hydroxyvitamin D levels and fracture risk in a community-based cohort of elderly men in Sweden. *Journal of Clinical Endocrinology and Metabolism* 2010;95(6):2637-2645.
147. Michaelsson K, et al. Plasma vitamin D and mortality in older men: a community-based prospective cohort study. *American Journal of Clinical Nutrition* 2010;92(4):841-848.
148. Vimaleswaran KS, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. *Lancet Diabetes Endocrinol* 2014;2(9):719-729.
149. Wang TJ, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet* 2010;376(9736):180-188.
150. Michaëlsson K, et al. Combined associations of body mass index and adherence to a Mediterranean-like diet with all-cause and cardiovascular mortality: A cohort study. *PLoS Medicine* 2020;17(9):e1003331.
151. Larsson SC, et al. Long-term dietary calcium intake and breast cancer risk in a prospective cohort of women. *American Journal of Clinical Nutrition* 2009;89(1):277-282.
152. Larsson SC, et al. Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men. *American Journal of Clinical Nutrition* 2008;88(4):1083-1087.
153. Michaelsson K, et al. Milk, Fruit and Vegetable, and Total Antioxidant Intakes in Relation to Mortality Rates: Cohort Studies in Women and Men. *American Journal of Epidemiology* 2017;185(5):345-361.
154. Hansson LM, et al. Diet-associated risks of disease and self-reported food consumption: how shall we treat partial nonresponse in a food frequency questionnaire? *Nutrition and Cancer* 2000;36(1):1-6.
155. Bergström L, et al. The food composition database KOST: the National Food Administration's information system for nutritive values of food [Swedish] *Vår föda* 1991;43:439-447.
156. Messerer M, et al. The validity of questionnaire-based micronutrient intake estimates is increased by including dietary supplement use in Swedish men. *Journal of Nutrition* 2004;134(7):1800-1805.
157. Creavin ST, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database of Systematic Reviews* 2016(1):Cd011145.
158. Ronnemaa E, et al. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. *Dementia and Geriatric Cognitive Disorders* 2011;31(6):460-466.
159. McKhann G, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34(7):939-944.
160. *American Psychiatric Association. Diagnostic and Statistic Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association; 1994.

161. Chui HC, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology* 1992;42(3 Pt 1):473-480.
162. Ludvigsson JF, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.
163. Information för Patientregistret, registerår 2019, version 3. 2020. (https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/statistik/information-for-patientregistret-registerar-2019.pdf). (Accessed Oct 24, 2021).
164. Brooke HL, et al. The Swedish cause of death register. *European Journal of Epidemiology* 2017;32(9):765-773.
165. World Health Organisation. International statistical classification of diseases and related health problems—10th revision. 5th ed. Geneva: World Health Organisation, 2016,
166. Feldman AL, et al. Accuracy and sensitivity of Parkinsonian disorder diagnoses in two Swedish national health registers. *Neuroepidemiology* 2012;38(3):186-193.
167. Hernán MA, et al. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *American Journal of Epidemiology* 2002;155(2):176-184.
168. Shrier I, et al. Reducing bias through directed acyclic graphs. *BMC Medical Research Methodology* 2008;8:70.
169. Syvänen AC, et al. Identification of individuals by analysis of biallelic DNA markers, using PCR and solid-phase minisequencing. *American Journal of Human Genetics* 1993;52(1):46-59.
170. Charlson ME, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987;40(5):373-383.
171. Quan H, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care* 2005;43(11):1130-1139.
172. Petrie A, et al. *Medical Statistics at a Glance*. Wiley Blackwell; 2009.
173. Harrell J, Frank, E. *Regression Modeling Strategies; With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer-Verlag; 2001.
174. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations. *International Journal of Obesity and Related Metabolic Disorders* 2000;24(9):1119-1130.
175. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Human Nutrition: Clinical Nutrition* 1985;39 Suppl 1:5-41.
176. Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation. *World Health Organization Technical Report Series* 1985;724:1-206.
177. Scarmeas N, et al. Nutrition and prevention of cognitive impairment. *Lancet Neurology* 2018;17(11):1006-1015.
178. Eskelinen MH, et al. Midlife healthy-diet index and late-life dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders Extra* 2011;1(1):103-112.
179. Berendsen AA, et al. Association of Adherence to a Healthy Diet with Cognitive Decline in European and American Older Adults: A Meta-Analysis within the CHANCES Consortium. *Dementia and Geriatric Cognitive Disorders* 2017;43(3-4):215-227.

180. Nooyens ACJ, et al. Adherence to dietary guidelines and cognitive decline from middle age: the Doetinchem Cohort Study. *American Journal of Clinical Nutrition* 2021.
181. Morris MC, et al. MIND diet slows cognitive decline with aging. *Alzheimers Dement* 2015;11(9):1015-1022.
182. Scarmeas N, et al. Mediterranean diet, Alzheimer disease, and vascular mediation. *Archives of Neurology* 2006;63(12):1709-1717.
183. Scarmeas N, et al. Mediterranean diet and Alzheimer disease mortality. *Neurology* 2007;69(11):1084-1093.
184. Hosking DE, et al. MIND not Mediterranean diet related to 12-year incidence of cognitive impairment in an Australian longitudinal cohort study. *Alzheimers Dement* 2019;15(4):581-589.
185. Haring B, et al. No Association between Dietary Patterns and Risk for Cognitive Decline in Older Women with 9-Year Follow-Up: Data from the Women's Health Initiative Memory Study. *Journal of the Academy of Nutrition and Dietetics* 2016;116(6):921-930.e921.
186. Hu EA, et al. Adherence to Dietary Patterns and Risk of Incident Dementia: Findings from the Atherosclerosis Risk in Communities Study. *Journal of Alzheimer's Disease* 2020;78(2):827-835.
187. Andreu-Reinón ME, et al. Mediterranean Diet and Risk of Dementia and Alzheimer's Disease in the EPIC-Spain Dementia Cohort Study. *Nutrients* 2021;13(2).
188. Schulze MB, et al. Food based dietary patterns and chronic disease prevention. *BMJ* 2018;361:k2396.
189. Duplantier SC, et al. A Critical Review of the Study of Neuroprotective Diets to Reduce Cognitive Decline. *Nutrients* 2021;13(7).
190. WHO Guidelines Approved by the Guidelines Review Committee. *Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines*. Geneva: World Health Organization © World Health Organization 2019., 2019.
191. Roberts RO, et al. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. *Journal of Alzheimer's Disease* 2012;32(2):329-339.
192. Volek JS, et al. Alternative Dietary Patterns for Americans: Low-Carbohydrate Diets. *Nutrients* 2021;13(10):3299.
193. Snellman G, et al. Determining vitamin D status: a comparison between commercially available assays. *PloS One* 2010;5(7):e11555.
194. Annweiler C, et al. Severe vitamin D deficiency is associated with advanced-stage dementia in geriatric inpatients. *Journal of the American Geriatrics Society* 2011;59(1):169-171.
195. Olsson E, et al. Vitamin D is not associated with incident dementia or cognitive impairment: an 18-y follow-up study in community-living old men. *American Journal of Clinical Nutrition* 2017;105(4):936-943.
196. Chen H, et al. 25-Hydroxyvitamin D Levels and the Risk of Dementia and Alzheimer's Disease: A Dose-Response Meta-Analysis. *Frontiers in Aging Neuroscience* 2018;10:368.
197. Jayedi A, et al. Vitamin D status and risk of dementia and Alzheimer's disease: A meta-analysis of dose-response (†). *Nutritional Neuroscience* 2019;22(11): 750-759.
198. Sommer I, et al. Vitamin D deficiency as a risk factor for dementia: a systematic review and meta-analysis. *BMC Geriatrics* 2017;17(1):16.
199. Maddock J, et al. Vitamin D and cognitive function: A Mendelian randomisation study. *Scientific Reports* 2017;7(1):13230.
200. Burgess S, et al. Avoiding bias from weak instruments in Mendelian randomization studies. *International Journal of Epidemiology* 2011;40(3):755-764.

201. Byberg L, et al. Reply to Y Mao and H Yu. *American Journal of Clinical Nutrition* 2017;106(2):698-699.
202. Byberg L, et al. Reply to WB Grant. *American Journal of Clinical Nutrition* 2017;106(2):700-701.
203. Maretzke F, et al. Role of Vitamin D in Preventing and Treating Selected Extraskeletal Diseases-An Umbrella Review. *Nutrients* 2020;12(4).
204. Bivona G, et al. Vitamin D and the nervous system. *Neurological Research* 2019;41(9):827-835.
205. Davey Smith G, et al. When Will Mendelian Randomization Become Relevant for Clinical Practice and Public Health? *JAMA* 2017;317(6):589-591.
206. Zhang Z, et al. Genetically Predicted Milk Intake and Risk of Neurodegenerative Diseases. *Nutrients* 2021;13(8).
207. Elwood PC, et al. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. *European Journal of Clinical Nutrition* 2004;58(5):711-717.
208. Vissers LET, et al. Milk intake and incident stroke and coronary heart disease in populations of European descent: A Mendelian Randomization study. *British Journal of Nutrition* 2021:1-25.
209. Michaëlsson K, et al. Serum retinol levels and the risk of fracture. *New England Journal of Medicine* 2003;348(4):287-294.
210. Nohr EA, et al. How to investigate and adjust for selection bias in cohort studies. *Acta Obstetricia et Gynecologica Scandinavica* 2018;97(4):407-416.
211. Ramnemark A, et al. Adequate vitamin D levels in a Swedish population living above latitude 63 degrees N: The 2009 Northern Sweden MONICA study. *International Journal of Circumpolar Health* 2015;74:27963.
212. Gerdhem P, et al. Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. *Osteoporosis International* 2005;16(11):1425-1431.
213. Yao S, et al. Demographic, lifestyle, and genetic determinants of circulating concentrations of 25-hydroxyvitamin D and vitamin D-binding protein in African American and European American women. *American Journal of Clinical Nutrition* 2017;105(6):1362-1371.
214. Gaig C, et al. When does Parkinson's disease begin? *Movement Disorders* 2009;24 Suppl 2:S656-664.
215. Marin C, et al. Olfactory Dysfunction in Neurodegenerative Diseases. *Current Allergy and Asthma Reports* 2018;18(8):42.
216. Reichmann H. Premotor Diagnosis of Parkinson's Disease. *Neuroscience Bulletin* 2017;33(5):526-534.
217. Gao H, et al. Evidence of a causal relationship between adiponectin levels and insulin sensitivity: a Mendelian randomization study. *Diabetes* 2013;62(4):1338-1344.
218. Heitmann BL, et al. Dietary underreporting by obese individuals--is it specific or non-specific? *BMJ* 1995;311(7011):986-989.
219. Gemming L, et al. Dietary under-reporting: what foods and which meals are typically under-reported? *European Journal of Clinical Nutrition* 2016;70(5):640-641.
220. Livingstone MB, et al. Markers of the validity of reported energy intake. *Journal of Nutrition* 2003;133 Suppl 3:895s-920s.
221. Becker W, et al. Under-reporting in dietary surveys--implications for development of food-based dietary guidelines. *Public Health Nutrition* 2001;4(2b):683-687.

222. Mattisson I, et al. Misreporting of energy: prevalence, characteristics of misreporters and influence on observed risk estimates in the Malmö Diet and Cancer cohort. *British Journal of Nutrition* 2005;94(5):832-842.
223. Nielsen BM, et al. Past and current body size affect validity of reported energy intake among middle-aged Danish men. *Journal of Nutrition* 2009;139(12):2337-2343.
224. Rautiainen S, et al. The validity and reproducibility of food-frequency questionnaire-based total antioxidant capacity estimates in Swedish women. *American Journal of Clinical Nutrition* 2008;87(5):1247-1253.
225. Rosell M, et al. Contribution of a manually coded part in an optically readable, precoded sevenday food record for the intake of energy, nutrients and foods. *Scandinavian Journal of Nutrition* 2003;47(3):123-131.
226. Willett WC, et al. Adjustment for total energy intake in epidemiologic studies. *American Journal of Clinical Nutrition* 1997;65(4 Suppl):1220S-1228S; discussion 1229S-1231S.
227. Rothman KJ, Greenland, S., & Lash, T.L. *Modern Epidemiology, 3rd Edition.* Philadelphia: PA: Lippincott, Williams & Wilkins; 2008.
228. Hernán MA, et al. A structural approach to selection bias. *Epidemiology* 2004;15(5):615-625.
229. Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Medicine* 2007;4(10):e297.
230. Kivipelto M, et al. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nature Reviews: Neurology* 2018;14(11):653-666.
231. Dhana K, et al. Healthy lifestyle and the risk of Alzheimer dementia: Findings from 2 longitudinal studies. *Neurology* 2020;95(4):e374-e383.

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