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IMPACT OF NUTRITIONAL STATUS AND DIET ON COGNITIVE DECLINE AND SURVIVAL

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Impact of nutritional status and diet on cognitive decline and survival

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my family

تقدیم به یگانگی وجود مادرم، پدرم و برادرانم
حامیان بی بدیل در لحظه لحظه زندگی ام

“The idea is to go from numbers to information to understanding.”

Hans Rosling

ABSTRACT

ENGLISH

This doctoral thesis investigated the complex relationship between nutritional status and survival and the impact of dietary intake on cognitive decline in older Swedish adults. The data used in the four studies (*I–IV*) in this thesis were derived from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). SNAC-K is a population-based prospective cohort study of 3,363 people aged ≥ 60 years in Stockholm, Sweden. The major findings are summarized below.

Study I. Nutritional status (by MNA-SF) and its relationship to survival were investigated using 11 years follow-up data. The multi-adjusted hazard ratios (95% confidence interval) of mortality was 2.40 (1.56–3.67) for those with malnutrition, and 1.49 (1.29–1.71) for those at risk for malnutrition. The median age at death was about 3 years younger in people with malnutrition and 1.5 years younger in people at risk for malnutrition than in those with normal nutritional status. Survival was shortened by an additional year in those who had suboptimal haemoglobin and/or albumin levels in addition to malnutrition or risk for malnutrition.

Study II. The hypothesis that the prudent diet may attenuate the adverse effects of the Western diet on cognitive decline was verified using 6-year follow-up data. The highest adherence to the prudent pattern was related to less MMSE decline (β : 0.106, $P=0.011$) than the lowest adherence, whereas the highest adherence to the Western pattern was associated with more MMSE decline (β : -0.156, $P<0.001$) than the lowest adherence. The decline associated with the Western diet was attenuated when accompanied by high adherence to the prudent pattern.

Study III. Six-year follow-up data were used to identify a dietary pattern index that predicts preserved cognitive function in a Nordic country, the Nordic Prudent Dietary Pattern (NPDP). Moderate (β : 0.139, 95% CI: 0.077–0.201) and high adherence (β : 0.238, 95% CI: 0.175–0.300) to the NPDP was associated with less cognitive decline than moderate or high adherence to four other dietary indices. High adherence to the NPDP was associated with the lowest risk of MMSE decline to ≤ 24 and had the greatest ability to predict such decline.

Study IV. The joint effect of a healthy diet and an active lifestyle on cognitive decline was examined using 6-year follow-up data. Moderate to high adherence to the NPDP was associated with less cognitive decline (β : 0.19, 95% CI: 0.14–0.24) than low adherence. This association became stronger when combined with moderate to intense physical (β : 0.34, 95% CI: 0.23–0.45), mental (β : 0.29, 95% CI: 0.21–0.37), or social (β : 0.27, 95% CI: 0.19–0.34) activity. An active lifestyle more than doubled the protective effect of the NPDP against cognitive decline, and further lowered the risk of MMSE decline to ≤ 24 by 30%.

Conclusions. Poor nutritional status (by MNA-SF) is presented in about a quarter of the older adults' population and associated with shorter survival, especially in those with suboptimal levels of biomarkers reflecting disease severity and inflammation (i.e. haemoglobin and albumin). Although high adherence to the Western diet is associated with cognitive decline, high adherence to the prudent diet may diminish these effects. Moderate to high adherence to the NPDP may predict better preserved cognitive function in Nordic countries than adherence to other healthy dietary indices. These findings lend further weight to the growing evidence of a link between a healthy diet and healthy brain aging. Finally, an active lifestyle may reinforce the protective effect of a healthy diet (i.e. NPDP) against cognitive decline.

Key words: nutritional status, biomarkers, survival, prudent dietary pattern, the Western dietary pattern, the Nordic Prudent Dietary Pattern, cognitive decline, active lifestyle, population-based cohort study

I denna avhandling har sambanden mellan kost och överlevnad samt kostens betydelse för kognitiv nedsättning hos äldre personer i Sverige studerats. Data som använts i avhandlingen, som består av fyra studier (I–IV), kommer från Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). SNAC-K är en populations-baserad prospektiv kohortstudie med 3,363 personer 60 år eller äldre i Stockholm. Nedan sammanfattas studiernas resultat.

Studie I. Risken för dödlighet var högre för undernärda personer (enligt MNA-SF kriterier) (HR: 2.40; 95% CI: 1.56–3.67) samt för personer med risk för undernäring (HR: 1.49; 95% CI: 1.29–1.71). Median- ålder för dödsfall var 3 respektive 1.5 år kortare för dem som bedömdes vara undernärda och för dem som bedömdes vara riskpersoner för undernäring jämfört med dem som bedömdes vara välnärda. Överlevnad förkortades ytterligare 1 år för personer med suboptimala biomarkörsnivåer (haemoglobin och/eller albumin) i kombination med undernäring eller risk för undernäring.

Studie II. Hypotesen att en så kallad hälsosam kost kan minska effekten av västerländsk kost på kognitiv nedsättning har verifierats med 6-års uppföljningsdata. Jämfört med dem som visade lägst följsamhet till en hälsosam kost, hade de med högst följsamhet till hälsosam kost mindre försämring på MMT (β : 0.106, $P=0.011$). Däremot, försämrades MMT mer hos dem som visade högst följsamhet till västerländsk kost (β : -0.156, $P<0.001$). Den försämring som kunde associeras till västerländsk kost blev mindre om kosten innehöll delar av en hälsosam kost.

Studie III. Nordic Prudent Dietary Pattern (NPDP), ett nordiskt kostindex/mönster som kan associeras till bevarad kognitiv förmåga kunde identifieras med 6-års uppföljningsdata. Moderat (β : 0.139, 95% CI: 0.077–0.201) och hög följsamhet till NPDP (β : 0.238, 95% CI: 0.175–0.300) var förenat med mindre kognitiv nedsättning jämfört med andra fyra använda kostindex. De med högst följsamhet till NPDP hade lägst risk för en försämring av MMT till ≤ 24 .

Studie IV. Effekten av att kombinera en hälsosam kost med en aktiv livsstil på kognitiv förändring har undersökts i 6-års uppföljningsdata. Moderat till hög följsamhet till NPDP var associerat till mindre kognitiv nedsättning (β : 0.19, 95% CI: 0.14–0.24) jämfört med lägre följsamhet till NPDP. Detta samband förstärktes i kombination med måttliga till intensiva fysiska (β : 0.34, 95% CI: 0.23–0.45), mentala (β : 0.29, 95% CI: 0.21–0.37), eller sociala (β : 0.27, 95% CI: 0.19–0.34) aktiviteter. En aktiv livsstil förstärkte den skyddande effekten av NPDP mot kognitiv nedsättning mer än två gånger, och minskade risken för MMT försämring till ≤ 24 med ytterligare 30%.

Slutsatser. Undernäring och risk för undernäring (enligt MNA-SF kriterier) förekommer i ungefär en fjärdedel av äldre människor och är associerat med kortare överlevnad, särskilt hos personer med suboptimala nivåer av biomarkörer kopplade till underliggande sjukdom och inflammation (haemoglobin och albumin). Även om en hög följsamhet till västerländsk kost är förenat med kognitiv nedsättning, kan en samtidig hög följsamhet till hälsosamkost minska dess negativa effekter på kognitionen. Jämfört med andra hälsosamma kostindex, tycks måttlig till hög följsamhet till NPDP bättre kunna bevara kognitiv förmåga hos personer i nordiska länder. Resultaten stödjer det ökande antalet bevis på ett samband mellan en hälsosam kost och ett hälsosamt hjärnåldrande. Slutligen kan en aktiv livsstil förstärka effekten av en hälsosam kost (d.v.s. NPDP).

Nyckelbegrepp: nutritionstatus, biomarkörer, överlevnad, hälsosam kost, västerländsk kost, the Nordic Prudent Dietary Pattern, kognitiv nedsättning, aktiv livsstil, populations-baserad kohortstudie

این پایان نامه دکترای تأثیر وضعیت تغذیه در بقاء و همچنین رابطه پیچیده دریافت‌های غذایی با عملکرد شناختی در افراد مسن سوئدی را مورد بررسی قرار می‌دهد. این پایان نامه براساس اطلاعات به کار گرفته شده از یک مطالعه ملی سوئدی بر روی پیری و مراقبت در SNAC-K Kungsholmen (SNAC-K) می‌باشد. SNAC-K یک مطالعه کوهورت آینده نگر مبتنی بر جمعیت است و شامل ۳۳۶۳ نفر افراد بالای ۶۵ سال ساکن استکهلم سوئد می‌باشد. این پایان نامه شامل ۴ مطالعه (I-IV) می‌باشد، و مهمترین یافته ها در زیر خلاصه شده است.

مطالعه I. وضعیت تغذیه (مشخص شده توسط MNA-SF) و ارتباط آن با بقاء با استفاده از اطلاعات ۱۱ سال پیگیری مورد بررسی قرار گرفت. نسبت خطر (Hazard Ratio) مرگ و میر و ۹۵٪ فاصله اطمینان (Confidence Interval, CI) برای سوء تغذیه ۲/۴۰ (۱/۵۶-۳/۶۷) و برای خطر سوء تغذیه ۱/۴۹ (۱/۷۱-۱/۲۹) بودند. متوسط سن مرگ و میر در افراد مبتلا به سوء تغذیه و خطر ابتلا به سوء تغذیه به ترتیب ۳ و ۱/۵ سال کمتر از کسانی بود که وضعیت تغذیه ای طبیعی داشتند. همچنین، سوء تغذیه یا خطر سوء تغذیه همراه با سطوح پایین هموگلوبین و یا آلبومین با ۱ سال بقا کوتاهتر مرتبط بود.

مطالعه II. در این مطالعه، این فرضیه که رژیم غذایی محافظت کننده (Prudent) ممکن است عوارض جانبی رژیم غذایی غربی را بر عملکرد شناختی کاهش دهد، با استفاده از داده های مطالعه کوهورتی با دوره پیگیری ۶ ساله مورد تأیید قرار گرفت. در مقایسه با کمترین پایداری به هر دو الگوی غذایی، بالاترین پایداری به الگوی غذایی محافظت کننده با کاهش کمتر MMSE در ارتباط بود ($\beta = 0.106$, $P = 0.001$). در حالیکه بالاترین پایداری به الگوی غذایی غربی با کاهش بیشتر MMSE ($\beta = 0.156$, $P = 0.001$) همراه بود. کاهش مرتبط با رژیم غذایی غربی هنگامی که با پایداری بالا به الگوی غذایی محافظت کننده همراه گردید، ضعیف شد.

مطالعه III. در این مطالعه با استفاده از داده های مطالعه کوهورتی با دوره پیگیری ۶ ساله، یک شاخص الگوی غذایی به نام الگوی غذایی محافظت کننده شمال اروپا (NPDP) شناسایی شد، که توانایی پیش بینی عملکرد شناختی حفظ شده در کشورهای شمال اروپا را دارد. پایداری متوسط ($\beta = 0.139$, 95% CI: 0.077-0.201) و بالا ($\beta = 0.238$, 95% CI: 0.175-0.300) به NPDP، در مقایسه با سایر چهار شاخص رژیم غذایی از پیش تعریف شده، با زوال شناختی کمتر همراه بود. پایداری بالا به NPDP با کمترین خطر زوال (≤ 24) MMSE همراه بود و بیشترین توانایی پیش بینی چنین کاهش را داشت.

مطالعه IV. در این مطالعه با استفاده از داده های مطالعه کوهورتی با دوره پیگیری ۶ ساله، اثر مشترک رژیم غذایی سالم و شیوه زندگی فعال در زوال شناختی مورد بررسی قرار گرفت. پایداری متوسط تا رو به بالا به NPDP نسبت به پایداری پایین، با زوال شناختی کمتر همراه بود ($\beta = 0.14$, 95% CI: 0.07-0.24). این ارتباط زمانی که با فعالیت متوسط تا شدید بدنی ($\beta = 0.34$, 95% CI: 0.23-0.45)، ذهنی ($\beta = 0.29$, 95% CI: 0.21-0.37)، و یا اجتماعی ($\beta = 0.27$, 95% CI: 0.19-0.34) همراه بود، قوی تر شد. یک سبک زندگی فعال، اثر پیشگیری کننده NPDP در برابر زوال شناختی را تا بیشتر از دو برابر تقویت می‌کند، و همچنین ۳۰٪ خطر ابتلا به کاهش MMSE تا ۲۴٪ را کاهش می دهد.

نتیجه گیری. سوء تغذیه و خطر ابتلا به سوء تغذیه (مشخص شده توسط MNA-SF) به ویژه در میان افراد مسن مبتلا به اختلال در نشانگرهای زیستی (هموگلوبین و آلبومین) بسیار شایع می‌باشد، و با بقا کوتاهتر در سالمندان مرتبط است. اگرچه پایداری بالا به رژیم غذایی غربی با زوال شناختی مرتبط است، پایداری بالا به رژیم غذایی محافظت کننده ممکن است اثرات نامطلوب آن بر عملکرد شناختی را کاهش دهد. در مقایسه با دیگر شاخص های غذایی سالم، پایداری متوسط تا رو به بالا به NPDP ممکن است پیش بینی بهتری از عملکرد شناختی حفظ شده در کشورهای شمال اروپا داشته باشد. این یافته ها از شواهد رو به رشدی که ارتباط بین رژیم غذایی سالم و پیری سالم مغز را نشان می‌دهند، حمایت می کند. در نهایت، یک سبک زندگی فعال ممکن است اثر حفاظتی یک رژیم غذایی سالم (به عنوان مثال، NPDP) را در برابر زوال شناختی تقویت کند.

واژگان کلیدی: وضعیت تغذیه، نشانگرهای زیستی تغذیه، بقاء، رژیم غذایی محافظت کننده و رژیم غذایی غربی، زوال شناختی، الگوی غذایی محافظت کننده شمال اروپا، سبک زندگی فعال، مطالعه کوهورت مبتنی بر جمعیت

LIST OF SCIENTIFIC PAPERS

This doctoral thesis is based on the following papers which will be referred to in the text by their Roman numerals (I–IV):

- I. **Shakersain B**, Santoni G, Faxén-Irving G, Rizzuto D, Fratiglioni L, Xu WL. Nutritional status and survival among old adults: an 11-year population-based longitudinal study. *Eur J Clin Nutr* 2016;70:320-325.
- II. **Shakersain B**, Santoni G, Larsson SC, Faxén-Irving G, Fastbom J, Fratiglioni L, Xu WL. Prudent diet may attenuate the adverse effects of Western diet on cognitive decline. *Alzheimer's & dementia* 2016;12:100-109.
- III. **Shakersain B**, Rizzuto D, Larsson SC, Faxén-Irving G, Fratiglioni L, Xu WL. Identifying a dietary pattern index that predicts preserved cognitive function in a Nordic country: a population-based cohort study (*Submitted*).
- IV. **Shakersain B**, Rizzuto D, Wang HX, Faxén-Irving G, Fratiglioni L, Xu WL. An active lifestyle reinforces the effect of healthy diet on cognitive decline (*Manuscript*).

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LIST OF ABBREVIATIONS

Alb	Albumin
ADL	Activities of Daily Living
APOE	Apolipoprotein E
BMI	Body mass index
BSD	Baltic Sea Diet
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
ESPEN	European Society of Clinical Nutrition and Metabolism
Hb	Haemoglobin
HDI	Healthy Diet Indicator
HEI	Healthy Eating Index
HR	Hazard ratio
MeDi	Mediterranean diet
MedDietScore	Mediterranean Diet Score
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MMSE	Mini-Mental State Examination
MNA	Mini-Nutritional Assessment
MNA-SF	Mini-Nutritional Assessment-Short Form
MUFA/SFA	Ratio between mono-unsaturated and saturated fatty acids
NPDP	Nordic Prudent Dietary Pattern
OR	Odds ratio
PUFA/SFA	Ratio between poly-unsaturated and saturated fatty acids
ROC	Receiver Operating Characteristic curve
SFFQ	Semi-quantitative Food Frequency Questionnaire
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
WHO	World Health Organization

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1 INTRODUCTION

1.1 GLOBAL AGING

The world population is aging at an accelerating pace as a consequence of the low fertility rates (below the replacement level of 2.1 births per woman), and increasing life expectancies. Over the next 15 years, the global number of people ≥ 60 years is projected to increase by around 56% reaching from 901 million to 1.4 billion.¹ Globally, one in every six people will be ≥ 60 years by 2030, and one in every five people will be ≥ 60 years by 2050.¹

The number of older people is expected to grow at a different pace in different geographical regions. The largest contributor between 2015 and 2030 will be Latin America and the Caribbean; their ≥ 60 years populations will increase 71%. During this period, Europe will face around a 23% increase in its number of older people, and despite a relatively lower growth rate in its old population, will remain the oldest continent with the largest old-age-dependency ratio (number of people ≥ 65 relative to those aged 15 to 64), around 50%, in 2060.^{1, 2} The current estimates and projections of the sex-specific number of people aged ≥ 60 in the world and in Europe by 2100 are illustrated in **Figure 1**.

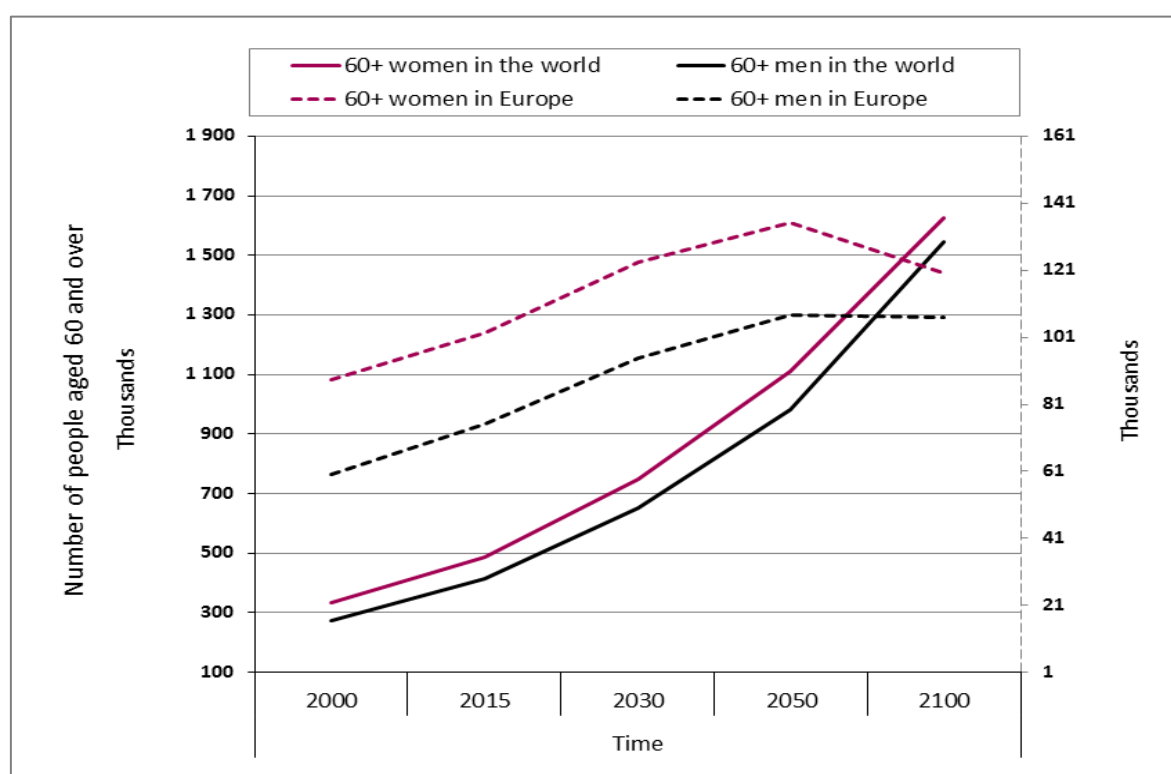


Figure 1. Global and European population aging projections. Data source: United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects: The 2015 Revision. Custom data acquired via website on August 15, 2016: <https://esa.un.org/unpd/wpp/DataQuery/>

Population aging is far from a new trend in Nordic countries, especially Sweden. In this Northern European country, 25.5% of the total population was ≥ 60 in 2015. This percentage is projected to reach 28.6% in 2030, and 29.6% in 2050.¹ **Figure 2** shows the Swedish population by age in 1960 and 2015 and the forecast age structure in 2060.

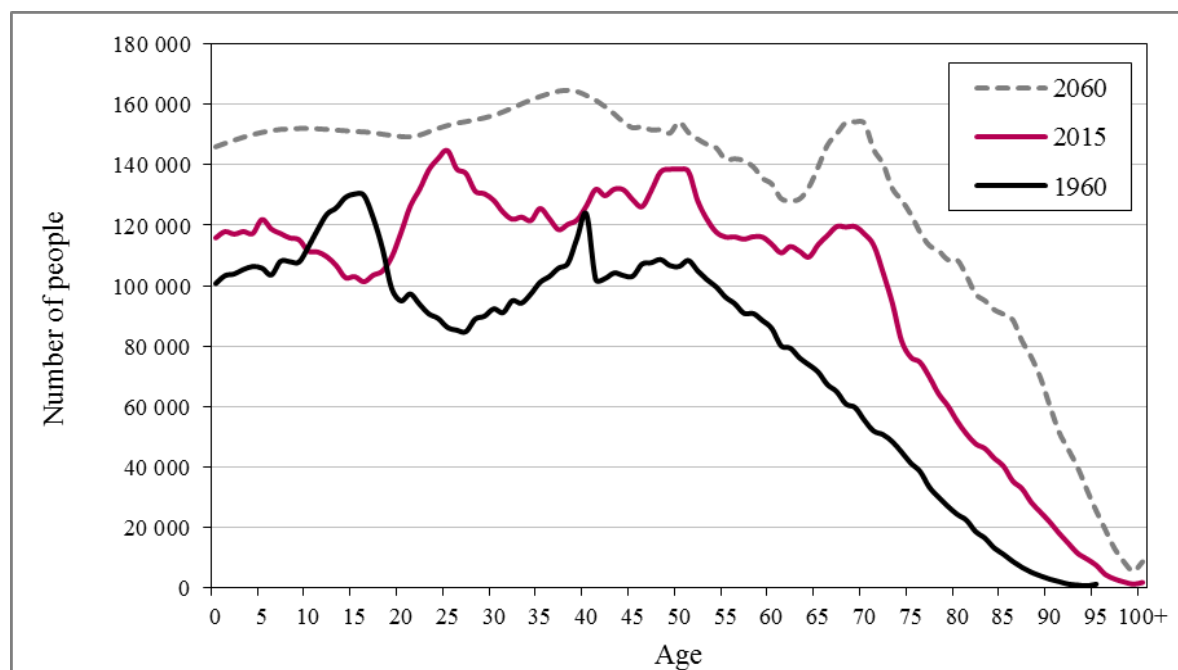


Figure 2. Population of Sweden by age in 1960 and 2015 and forecast age structure in 2060. Data source: Statistics Sweden, Population projections. Accessed on August 15, 2016.

Although the expansion of aging populations implies a triumph of medical, social, and economic advancement, it has an impact on health dynamics (disease patterns and prevalence).³ Following the increase in life expectancy, and lower mortality from chronic conditions in most parts of the world, potential interaction between morbidity and mortality trends have been the basis of much research on health trends.⁴ Globally, dementias' contribution to years of healthy life lost (DALYs) was 0.91% in 2013, a number that is expected to increase by 1.5% annually. In western European countries with a higher proportion of older people, this contribution was 3.62% in 2013, and the estimated annual increase was 1.66%.⁵ A longer life is an opportunity for further personal life achievements and contributions to the betterment and viability of the society; however, the likelihood and efficiency of such achievements and contributions depends heavily on one key factor – health.⁶

Multi-systemic physiological and psychological changes occur with aging. They involve sensory abilities (e.g. hearing, vision, taste, etc.), the motor system (e.g. muscle sarcopenia), and cognition.⁷ There is a “gray zone” between the state of “normal” aging and pathological aging.⁷ Compromised health (i.e. reduced physical and mental capacity) could turn the extended years of life from an opportunity into a negative challenge for older people and for

societies,⁶ so the growing proportion of aged people can increase the extent of need for health and social services. Thus, counterbalancing the progression of degenerative diseases in old age is a high public health priority. In this case, identification of factors that help people age as normal as possible and maintain their physical, social, and psychological functioning is vital.

1.2 NUTRITIONAL STATUS IN OLD AGE

Nutrition has long been considered critical to promoting healthy aging. Nutritional status is people's state of health in relation to their intake and utilization of food and nutrients. Nutritional status and health may have a bidirectional association in old age. On one hand, as people get older, various physiological and pathological changes may occur in their bodies that could influence their nutritional intakes and efficiency of nutrients utilization. On the other hand, impaired nutritional status after a decrease in food intake or nutrients absorption could aggravate existing disease states and worsen the health status of older adults. Recent estimates suggest that around 33 million people in Europe are affected by disease-related poor nutritional status, a mostly preventable condition that costs governments up to €170 billion annually.⁸ Thus, timely detection and treatment of nutritional problems in older people and possibly their underlying causes are critical for healthy aging.

1.2.1 Malnutrition

Definition. Malnutrition includes both over- and undernutrition. However, in the older populations of developed countries, it mainly refers to age- or disease-related undernutrition. Although for decades there has not been any internationally accepted definition of malnutrition, the European Society of Clinical Nutrition and Metabolism (ESPEN) has recently defined malnutrition due to starvation, disease, or aging as “a state resulting from lack of uptake or intake of nutrition leading to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease”.⁹

Prevalence. The number of people at risk for compromised nutrition may increase with the growth of older populations. In the absence of a standardized definition of malnutrition and criteria for its diagnosis, estimates of the prevalence of malnutrition in older adults have varied, depending on the study settings and levels of care, and the screening/assessment tools used.⁹ The reported overall prevalence of malnutrition in community-dwelling older people in Europe and North America is between 1% and 15%. It ranges from 25% to 60% in geriatric care facilities and is estimated to be around 35% to 65% in hospitalized older patients.¹⁰

Screening and assessment. Poor nutritional status is prevalent among older adults, both those living at home and those living in care settings, and in many cases is undiagnosed. Because being at risk for compromised nutrition increases the chance of developing malnutrition, preventive screening for the risk for malnutrition is as important as diagnosis

and treatment of malnutrition. The commonly used criteria for assessing nutritional status in old age can be summarized as follows: 1) weight loss (as a consequence of a negative energy balance after reduced food intake or increased energy expenditure), 2) anthropometric measures (including body mass index [BMI], calf circumference, arm muscle circumference, and triceps skinfold), 3) body composition (i.e. fat free mass and fat mass, which can be objectively measured by bioelectrical bio-impedance analyses, dual energy x-ray absorptiometry, computed tomography, ultrasound, or magnetic resonance imaging), 4) anorexia (i.e. loss of appetite that is one of the major mechanisms behind weight loss and is a common complication of disease, medication, and aging), 5) reduced food intake (either self-reported or quantified), and 6) serum concentration of albumin as a marker of visceral protein; inflammatory markers like C-reactive protein and white blood cell count to assess inflammation status as an important etiologic factor for malnutrition; measures of blood or urine concentrations of nutrients or their metabolites, or specific metabolic responses to examine individual vitamins and minerals status.^{9, 11} There are different opinions on whether functional measures of strength and power, in addition to abovementioned factors, need to be considered in nutritional assessments of older people.⁹

Given the multifactorial nature of malnutrition, it seems unlikely that application of any single criterion can accurately detect risk of malnutrition in older adults. Thus, a systematic and comprehensive approach to screening and assessing risk and accurately diagnosing malnutrition and its underlying causes is necessary for planning efficient allocation of nutrition interventions and treatments. Screening to identify nutritional concerns is the first step in the nutritional care process.^{9, 12} The main ideas behind nutritional risk screening are to identify people who need thorough nutritional assessment and support (i.e. those who are at risk) to prevent the development of malnutrition and to treat existing malnutrition in a timely fashion. In the absence of a gold standard for nutritional evaluation, several nutritional screening tools, each of which includes a different set of variables, have been designed and validated in different settings.

According to the ESPEN, BMI, unintentional weight change, and food intake decline are the three factors most predictive of malnutrition and need to be included in all nutritional screening tools.¹³ Screening tools need to be quick and easy to administer, cost-effective, acceptable to the target population, and sensitive and specific enough for the purpose for which they are being used (to be valid). They also need to generate consistent test scores from one occasion to the other (to be reliable). Because of the differences in nutritional concerns and health status of different older populations in different settings, the screening tool must be valid with regard to age, sex, and ethnicity of the target population and the particular setting in which it will be used.¹⁴ There are few malnutrition screening tools with acceptable reliability and validity test results in community-dwelling older adults.¹⁴

The full Mini-Nutritional Assessment (MNA) questionnaire, which has 18 items, is one of the tools frequently used in older adults in all settings. It was first designed and validated in 1994

as part of the standard geriatric evaluation to assess nutritional status of frail older individuals aged ≥ 65 years.^{15,16} The 10 to 15 minutes needed to complete the MNA, though, has made it a less feasible approach in some acute care settings.¹⁷ Thus, the six items short form of MNA (MNA-SF) was developed in 2001 to reduce the burden of time needed for training the staff and administering the tool.¹⁸ The MNA-SF is 97.9% as sensitive, 100% as specific, and 98.7% as diagnostically accurate in predicting malnutrition as the full MNA but takes only about 4 to 5 minutes to complete.^{18, 19} The MNA-SF is the most widely validated and used screening tool in older adults aged ≥ 65 of all settings. In a review of commonly used screening tools, MNA-SF appeared to be the most appropriate screening tool in older community-dwellers.¹⁴

This shorter version defines the nutritional status of each person on the basis of information about their appetite loss/eating difficulties, weight loss, mobility status, stress/acute diseases, neuropsychological problems, and BMI. The total score ranges between 0 and 14.²⁰ After it was validated in 2009, the MNA-SF was approved for use as a stand-alone nutritional screening tool.¹⁷ With the help of either the caregiver or a proxy, it can even be administered to people who are bedridden or those who have dementia, groups initially excluded from nutritional screening procedures.¹⁷ As in the full MNA, MNA-SF divides people into three groups by total score: “normal” nutritional status (12–14); “risk for malnutrition” (8–11); and “malnutrition” (0–7).¹⁷

Despite the high prevalence of malnutrition, nutritional assessment and support usually rank low on the list of health evaluation and treatment priorities.²¹ The MNA-International Group recommends repeating nutritional risk screening by MNA-SF at least once a year in those living in the community.^{17, 20} In those in the hospital or long-term care, the MNA-SF should be repeated at least once every three months or whenever a change in clinical condition may affect nutritional status.^{17, 20} Further in-depth nutritional assessment, close weight monitoring, and nutritional interventions (diet enhancement and oral nutritional supplementation) are recommended in those identified by the MNA-SF as malnourished or at risk for malnutrition with unintentional weight loss.²⁰

1.2.2 Nutritional status and mortality

Although it is not conclusive, existing evidence suggests that a maximum of one-third of the variation in survival might be attributable to genetic factors.²² Thus, most of the inter-individual variation in length of life appears to be explained by environmental factors, including nutrition.²² In a recent review on the association between geriatric syndromes (multiple comorbidities, disability, frailty, malnutrition, cognitive impairment, chronic inflammation, and impaired homeostasis) and survival among community-dwelling people aged ≥ 65 , malnutrition and impaired homeostasis exerted twice the influence of factors such as multiple comorbidities and frailty on mortality.²³ In this expert consensus-based review, malnutrition was defined mainly as unintentional weight loss or low BMI, followed by low

albumin, anemia, and micronutrients deficiencies. The definition of impaired homeostasis also included low albumin (Alb), high C-reactive protein (CRP), and a few other factors.²³

Table 1 represents a summary of 13 longitudinal studies of the association between nutritional status (according to MNA-SF) and all-cause mortality. Only two are population-based; the majority used hospital or nursing-home data. People classified as malnourished by MNA-SF have an approximately three to five times higher chance of dying than those with normal nutritional status.

One of the major concerns in malnutrition management is to identify the people that will benefit the most from nutritional interventions; i.e. those at higher risk of adverse effects related to poor nutrition. Biochemical markers such as visceral proteins (e.g. serum Alb) and inflammatory activity measures (e.g. CRP) were traditionally examined as indicators of nutritional status. However, despite their wide clinical use, the use of visceral protein and inflammatory marker measures as nutritional indicators is questionable, as the measures of serum Alb are subject to further reduction, and measures of CRP are subject to increase under inflammatory conditions. Thus, low levels of serum Alb or high levels of CRP are, instead, good indicators of disease severity. The important role of inflammation in age- or disease-related catabolism can be taken into account as an etiologic factor in diagnosis and management of compromised nutritional status.⁹ In fact, these biochemical measures could be considered in predicting the probability of a better or worse outcome (e.g. survival vs. death) in relation to nutritional status, and thus, in prioritizing those in greater need of further clinical assessments and care.

1.2.3 Knowledge gap

As previously mentioned, predictions of adverse outcomes by nutritional screening tools might be improved if the screening results are combined with information on etiological factors behind compromised nutritional status, such as measures of visceral proteins or inflammatory markers. Moreover, limited care resources (material and human) need to be allocated on the basis of the severity of problems. Although the association between mortality in older people and biomarker levels, and between mortality in older people and nutritional status has been studied independently,²⁴⁻²⁷ data on combining nutritional screening and biochemical measures to predict mortality and thus to better prioritize those in need of nutritional interventions are scarce.

Table 1. Summary of major longitudinal studies on the association between nutritional status, assessed with the MNA-SF, and mortality

Author & year	Population	Follow-up (year)	Malnutrition at baseline (%)	Mortality at follow-up (%)	Mortality relative risk	Covariates
Community-dwellers						
Wang et al. 2013 Taiwan ²⁸	N=2872 Age ≥65 Sex (F) 45.3%	4	At risk: 19% Malnutrition: 3.5%	20.1%	At risk of malnutrition HR=1.67 (1.37-2.03) Malnutrition HR=3.00 (2.20-4.11)	Age, sex, education, living arrangement, lifestyle, chronic diseases, ADL
Kiesswetter et al. 2014 Germany ²⁷	N=309 Age ≥80 Sex (F) 64%	1	At risk: 41.1% Malnutrition: 4.9%	14.6%	At risk of malnutrition HR=2.21 (1.02-4.75) Malnutrition HR=3.27 (1.34-8.02)	Age, chronic diseases, care level, ADL
Nursing home						
Ulger et al. 2013 Turkey ²⁹	N=534 Age 79 (mean) Sex (F) 65%	1.5	At risk: 53.6% Malnutrition: 5.9%	22.1%	Mortality: Normal=9.9% At risk=24.0% Malnutrition=40.8%	Not reported
Törmä et al. 2013 Sweden ³⁰	N=172 Age 86 (mean) Sex (F) 70%	1	At risk: 63% Malnutrition: 30%	24%	Malnutrition OR=2.37 (1.07-5.26)	Age, Charlson Comorbidity Index score
Lilamand et al. 2015 France ³¹	N=773 Age=86 (mean) Sex (F) 74%	1	At risk: 58.7% Malnutrition: 5.7%	17.5%	At risk of malnutrition HR=1.91 (0.77-4.76) Malnutrition HR=4.39 (1.65-11.7)	Age, sex, respiratory diseases, Abbreviated Mental Test score
Clinical settings						
Vischer et al. 2012 Switzerland ³²	N=444 Age=85 (mean) Sex (F) 74%	4	At risk: 50.5% Malnutrition: 25%	51%	At risk of malnutrition HR=0.79 (0.56-1.12) Malnutrition HR=0.89 (0.59-1.36)	Age, sex, BMI, albumin, Cumulative Illness Rating Scale-Geriatrics
Sargento et al. 2013 Portugal ³³	N=50 Age 74 (mean) Sex (F) 30%	1	At risk: 20% Malnutrition: 7.6%	12%	At risk of malnutrition HR=0.64 (0.07-5.48) Malnutrition HR=8.00 (0.92-69.2)	Not reported

Gentile et al. 2013 France ³⁴	N=157 Age 84 (mean) Sex (F) 58.6%	0.3	Malnutrition: 29%	14.6%	Malnutrition OR=20.2 (5.74-71.3)	Age, sex, living alone
Yost et al. 2014 USA ³⁵	N=162 Age >18 Sex (F) not shown	2.7	At risk: 47.5% Malnutrition: 0.9%	40.7%	Higher mortality for malnutrition/at risk of malnutrition ($P < .0001$)	Not reported
Bell et al. 2014 Australia ³⁶	N=142 Age ≥ 50 Sex (F) 68%	0.3	Normal/at risk: 73% Malnutrition: 27%	15%	Normal/at risk (Ref.) Malnutrition OR =2.39 (0.77-6.95)	Age, usual place of residency, co-morbidities, time-to-surgery
Asiimwe et al. 2015 Uganda ³⁷	N=318 Age >18 Sex (F) 48%	0.1	At risk: 33% Malnutrition: 59%	37%	Malnutrition HR=2.7 (1.3-5.9)	Age, sex, education, infectious diseases, blood pressure
Nuotio et al. 2016 Finland ³⁸	N=472 Age ≥ 77 Sex (F) 75%	0.3	At risk: 42% Malnutrition: 9%	19%	At risk of malnutrition HR=1.32 (0.77-2.26) Malnutrition HR=2.16 (1.07-4.34)	Age, sex, living condition, mobility, general health, memory impairment
Koren-Hakim et al. 2016 Israel ³⁹	N=215 Age 83 (mean) Sex (F) 71%	3	At risk: 44.2% Malnutrition: 1.6%	36.7%	Mortality: Normal=22.1% At risk= 40% Malnutrition=50.5%	Not reported

Abbreviation: **ADL**=Activities of Daily Living, **BMI**=Body Mass Index, **HR**=Hazard Ratio, **MNA-SF**=Mini-Nutritional Assessment-Short Form, **N**=Number; **OR**=Odds Ratio

1.3 COGNITIVE DECLINE IN AGING

Aging is accompanied by an overall progressive physiological decline of bodily reserves, which leads to diminished ability to generate adaptive responses and sustain homeostasis.⁴⁰ Subsequent decrease in the overall resistance to stressors may lead to age-related pathologies, and ultimately leads to death.⁴⁰ One example is age-related structural brain changes, and consequently, of cognitive deficits. Cognition is “the mental action or process of acquiring knowledge and understanding through thoughts, experiences, and the senses”.⁴¹ It includes different mental processes (or cognitive domains), mainly memory, executive functions, attention, perceptual/processing speed, visuospatial ability, and language abilities.⁴²

Age-related biological alterations that affect our cognitive function start in early midlife and usually continue well into late life.⁴³ A bit fewer than half of the adults aged ≥ 65 years can be diagnosed with some sort of cognitive dysfunction.^{43, 44} Without proper screening, follow-up, and intervention, deteriorating cognition, together with structural and functional brain changes that occur with aging may interfere with the capacity for independence in activities of daily life and ultimately lead to severe cognitive impairment and dementia (**Figure 3**).

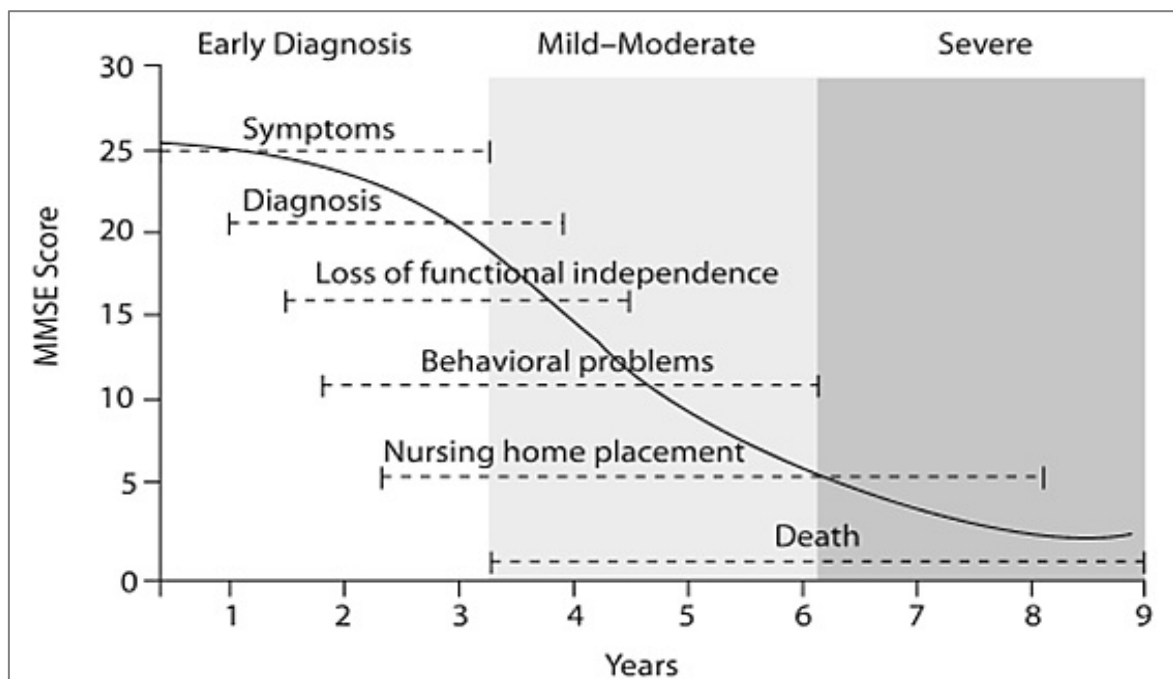


Figure 3. Natural history of cognitive decline and its progression to dementia (adapted from Geldmacher et al. 2006)⁴⁵

Cognitive function can be evaluated with test of global cognition or more comprehensive neuropsychological tests that assess specific cognitive domains. The Mini-Mental State Examination (MMSE) was introduced about 40 years ago.⁴⁶ It is a standard, validated tool, and is the most commonly used screening tool for cognitive impairment and dementia. The MMSE contains 11 questions regarding orientation to time and place, registration (ability to

remember), attention and calculation (ability to follow verbal commands regarding counting and spelling), recall, language (ability to name objects, repeat sentences, follow written commands, and spontaneously write a sentence), and visuo-constructional skills (copying a relatively complex figure; that is, two interlocking pentagons).^{46, 47} Cutoffs for defining cognitive impairment have been chosen differently, depending on the study aims and the age and educational levels of the study populations.⁴⁸ Traditionally, the MMSE score of ≤ 24 has been used in dementia screening as a cut-off with sensitivity of 87% and specificity of 82%.^{42, 47}

Because aging is usually accompanied by a varying type and extent of physiological and biological changes, distinguishing between normal age-related cognitive decline and abnormal, pathological cognitive decline (especially the early stages of such decline) is not easy. Over the lifespan, there is a dynamic interplay between neurodegenerative or cognition-impairing factors, and factors that improve neuroplasticity and consequently cognitive functioning.⁴⁹ Many risk and protective factors for cognitive function and dementia have been proposed and investigated. However, the results of studies have varied, and the relevance of some of the proposed factors is open to debate. A summary of common risk and protective factors for cognitive decline is presented in **Table 2**. There is currently no cure for dementia, and available treatment strategies offer mainly symptomatic benefits. Thus, strategies to prevent or delay the onset of dementia by slowing down the progression of cognitive decline through changes in lifestyle factors, such as diet, are highly important.

Table 2. Summary of major risk and protective factors for cognitive health⁵⁰

RISK FACTORS	PROTECTIVE FACTORS
Older age	
Genetic factors	Genetic factors
Familial aggregation	Some genes proposed (e.g. <i>APOE</i> ϵ 2 & <i>APP</i>)
<i>APOE</i> ϵ 4 allele	Psychosocial factors
Other susceptibility genes (e.g. <i>CR1</i> & <i>PICALM</i>)	High education and socioeconomic status
Vascular and metabolic factors	High work complexity
Atherosclerosis	Rich social network and social engagement
Cerebral macro- and micro-vascular lesions	Mentally stimulating activities
Cardiovascular diseases	Lifestyle factors
Diabetes and pre-diabetes	Physical activity
Midlife hypertension	Mediterranean diet
Midlife overweight and obesity	Polyunsaturated fatty acids and fish fats
Midlife high serum cholesterol	Vitamin B6, vitamin B12, and folate
Lifestyle factors	Antioxidant vitamins (A, C, E)
Sedentary lifestyle	Vitamin D
Smoking	Light to moderate alcohol intake
Diet rich in saturated fat	Drugs
Deficiencies in vitamin B6, B12, and folate	Antihypertensive drugs
Hyperhomocysteinaemia	Statins
Heavy alcohol drinking	Hormone replacement therapy
Other factors (e.g. depression, brain injuries)	Non-steroidal anti-inflammatory drugs

Abbreviations: *APOE*=Apolipoprotein E, *APP*=amyloid precursor protein, *CR1*=complement component receptor 1, *PICALM*=phosphatidylinositol-binding clathrin assembly protein.

1.4 DIETARY PATTERNS AND COGNITIVE DECLINE

1.4.1 Dietary patterns

Studies on single nutrients or foods are valuable in detecting potential influential dietary components and determining biological mechanisms underlying the risk or protective effects of dietary factors.⁵¹ However, they usually fail to 1) consider the interactive (i.e. synergistic/opposing) effects of multiple foods/nutrients in the complex combination of foods people eat as daily meals and snacks, 2) disentangle the effect of inter-correlated nutrients in the diet, 3) detect the small effects of single nutrients/food items, and 4) control for the confounding effect of overall dietary pattern on single nutrient/food association with the outcome.⁵¹

Thus, the cumulative effect of different dietary components has received special attention, and the relationship between different dietary patterns and various chronic disorders has been examined.^{51, 52} In recent years, several dietary patterns have been empirically derived, and their relationship to cardiovascular diseases, cancer, or mortality has been studied.⁵³ A well-known example of a healthy eating pattern is the Mediterranean diet, which has been associated with reduced risk of premature death.⁵⁴ The American Healthy Eating Index (HEI), which is based on adherence to the U.S. dietary guidelines, is inversely associated with all-cause mortality in elderly people in the United States.⁵⁵ However, studies on the international level require the operationalization of globally applicable dietary guidelines. Therefore, the 1990 World Health Organization (WHO) guidelines for a healthy diet for the prevention of chronic diseases and subsequent increase of life expectancy were translated into the Healthy Diet Indicator (HDI).⁵⁶ However, we still have a long way to go before concluding whether any of the proposed diets/dietary guidelines really contain a common set of dietary principles for prevention of all prevalent health conditions in all populations.

During the last decade, overall dietary pattern analysis has been in the spotlight as a complementary approach to the previous reductionist assessments of single food component. For this purpose, hypothesis-driven or *a-priori* approaches and data-driven or *a-posteriori* methods have been proposed and used. *A-priori* approaches include dietary scores or indices that are based on general dietary guidelines or hypothetical diet-disease relationships. *A-posteriori* approaches include dietary patterns that are identified on the basis of available dietary data that reflect the true eating habits of the population, regardless of any pre-existing knowledge about the diet-disease relationships. The latter eating patterns are mainly captured with statistical methods such as principal component and cluster analyses.^{57, 58} Each of these approaches has advantages and disadvantages. For instance, in principal component analysis, the highly correlated foods aggregate to create sets of underlying independent factors (i.e. dietary patterns) that explain as much variation in dietary data as possible. However, the researcher makes a series of subjective decisions during such analysis that might affect the final results, including the food groupings, number of food groups included in the analysis, energy-adjustment and standardization of food variables, the factor loading cutoffs and number of factors to retain, interpreting and labeling the factors, and more.⁵⁹ On the other hand, dietary indices are mainly proposed on the basis of the best available scientific evidence of diet-disease associations. Although it is possible to reproduce and compare the dietary indices, they are often modified as knowledge around a specific topic grows.⁶⁰

1.4.2 Relation between dietary patterns and cognitive decline

With the expansion of aging populations, identifying the factors that contribute the most to the existing large variation in cognitive functioning in older individuals has become a high public health priority. In recent decades, many epidemiological studies, including 17 cross-sectional and 25 longitudinal studies, have examined the association between dietary patterns

(or dietary indices) and cognitive decline or impaired cognitive function and have suggested relationships between dietary intakes and cognitive decline or cognitive impairment.

Of the longitudinal studies reviewed for thesis, 18 have investigated the association between the Mediterranean diet and cognitive decline, and 9 of them have shown that this dietary pattern is significantly associated with reduced cognitive decline. Four other studies separately examined the association between MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay), DASH (Dietary Approaches to Stop Hypertension), the Nordic Diet, and the modified Alternative-HEI and cognitive decline. A summary of the findings of these longitudinal studies about dietary patterns and cognition is presented in **Table 3**. The dietary pattern most commonly studied in relation to cognitive health is the Mediterranean diet, either as an index (e.g. MeDi, MedDietScore) or as an identified factor (i.e. eating pattern).^{61, 62} Although the current evidence mainly supports the intake of plant-based foods (as in the Mediterranean diet), findings seem to be more consistent in southern European populations than in populations in other parts of the world. Data from North America and from the very few studies in Northern Europe have yielded contradictory results. Inconsistent findings highlight the need for methodological improvements to assess dietary intake and cognitive functioning more accurately and to more closely investigate dietary intake and its relationship with cognitive functioning at the regional level.

1.4.3 Role of leisure activities in the association between diet and cognitive decline

Because up to half of all dementia cases may be attributable to modifiable lifestyle-related factors,⁶³ many researchers have attempted to address the effects of lifestyle factors on the risk of developing dementia.⁶⁴ Indeed, physical, studies show that mental, and social activities are associated with reduced risk of cognitive impairment and dementia,^{65,66} despite some inconsistencies in findings.⁶⁷

Lifestyle is a complex set of interrelated behaviors and exposures. We can speculate that people with healthier eating habits are more health-conscious in general and tend to have an active lifestyle. Epidemiological studies suggest that lifetime exposures to healthy lifestyle factors may increase cognitive reserve or resilience.^{64, 68} The interplay between multiple lifestyle factors may have a variety of effects on underlying neurodegenerative processes in the brain.⁶⁹

Although diet is among the lifestyle factors that may have the most influence on maintaining healthy aging, the role of other lifestyle traits and the magnitude of the potential joint effect of these factors on cognition are public health topics of great interest. Previous studies have investigated the effects of cognitively stimulating activities,⁷⁰ physical activity,⁶⁵ and social engagement⁷¹ on cognitive function independently and in combination⁷²⁻⁷⁴. However, the joint effect of eating patterns and leisure activities in old age on cognitive functioning has not

yet been well studied. To the best of our knowledge, only two studies have examined the combined effect of diet and leisure activities on the risk of dementia; they have found that healthy eating habits together with physical⁷⁵ or social activities⁶⁹ could reduce the risk of Alzheimer's disease and dementia.

1.4.4 Knowledge gap

A number of points need to be taken into account before drawing any conclusions from this short review of the literature about the association between dietary patterns and cognitive decline. First, dietary intake of several nutrients (such as vitamin E, vitamin D, B vitamins, vitamin C, polyunsaturated omega-3 fatty acids, polyphenols),^{76, 77} and food items (such as fruits, vegetables, wine, tea, coffee, cocoa, and fish)⁷⁸ have been independently associated with better cognition and brain health. Although the results of randomized controlled trials have been promising, overall, these trials have not yet provided strong evidence that any single nutrient or food can prevent cognitive decline.^{79, 80} Understanding the true association between diet and cognition is challenging because both nutritional and neurological sciences are complex, and their related methodologies have limitations.⁸¹ One of the limitations of these studies is overlooking the fact that people in real-life situations (especially those who are relatively healthy) may simultaneously adhere to different types of diets and consume different combinations of healthy and unhealthy foods. The contradicting effects of the foods people consume on their health might lead to differences in estimated size and direction of associations between diet and cognition in different studies.

Second, food intake is constantly influenced by various factors, including health status; cultural traditions; individual preferences and beliefs; socio-economic status; and geographical, social, and environmental factors.⁸² Even differences in genetic background between populations might lead to varying tastes for food and different food preferences.⁸³ Thus, one possible reason for discrepancies in the results of studies of the Mediterranean diet and cognition in geographical areas other than the Mediterranean region could be that this specific eating pattern may not be well-adapted in those areas, for instance in the Northern European population. In the absence of specific dietary guidelines on preventing cognitive decline, significant findings about food-cognition associations need to be considered in constructing diet quality indices. However, the “one size fits all” approach of recommending one specific diet for preserving cognitive function in all people may not be optimal. The current dietary recommendations may still need to be modified to fit the circumstances of all populations.

Third, dietary habits are only one component of a healthy lifestyle. Another important element is leisure activity. More health-conscious individuals often engage in not one but several healthy behaviors. Thus, investigations aimed at finding the multiple dimensions of lifestyle that are associated with disease risk are important. Nevertheless, many studies focus on specific individual factors.

In summary, there is increasing interest in the association between dietary patterns and cognitive function because the topic is relevant both to public health and to advancing scientific understanding. Exploring this association may help identify new pathways leading to preserved cognitive function. Keeping the aforementioned knowledge gaps in mind, we initiated a project that is summarized in this thesis.

Table 3. Major population-based longitudinal studies on the association between dietary patterns and cognitive decline

Author, Year	Population	Follow-up (year)	Dietary data	Dietary patterns	Cognitive measure	Results	Covariates
Scarmeas et al. 2006 USA ⁸⁴	N=2258 Age ≥65 Sex (F) 68% Community	4	61 item- FFQ (energy-adjusted)	MeDi (0-9) (veg, legumes, fruits, cereals, fish, meat, dairy, MUFA/SFA, alcohol)	Z-score of a composite measure (12 tests)	$\beta=0.003$ ($p=0.047$)	Age, sex, education, BMI, APOE $\epsilon 4$, energy intake, smoking, comorbidity
Psaltopoulou et al. 2008 Greece ⁸⁵	N=732 Age ≥60 Sex (F) 65% Community	8	150 item- FFQ	MeDi (0-9) (veg, legumes, fruits and nuts, cereals, fish, meat, dairy, MUFA/SFA, alcohol)	MMSE	No significant association	Age, sex, education, BMI, energy intake, marital status, lifestyle, diabetes, hypertension, depression
Féart et al. 2009 France ⁸⁶	N=1410 Age ≥65 Sex (F) 63% Community	5	148 item- FFQ	Mediterranean diet score (0-9) (veg, legumes, fruits, cereal, fish, meat, dairy, MUFA/SFA, alcohol).	Number of errors in MMSE and some domains	$\beta = -0.006$ (fewer errors)	Age, sex, education, BMI, APOE $\epsilon 4$, energy intake, marital status, lifestyle, diabetes, CVD
Wengreen et al. 2009 USA ⁸⁷	N=3634 Age ≥65 Sex (F) 57% Community	11	142 item- FFQ	RFS (fruits, veg excluding potatoes, lean meat, fish, low-fat dairy, whole grains) Non-RFS (sum of 23 non-recommended foods including highly processed energy-dense foods)	3MS (scored 0-100)	RFS 4 th quartile had ~2 points less decline ($p=0.0013$) No association for non-RFS	Age, sex, education, BMI, APOE $\epsilon 4$, energy intake, lifestyle, ADL, diabetes, CVD, supplement use
Gu et al. 2010 USA ⁸⁸	N=1219 Age ≥65 Sex (F) 67% Community	4	61 item- FFQ (energy-adjusted)	MeDi (0-9) (veg, legumes, fruits, cereals, fish, meat, dairy, MUFA/SFA, alcohol)	Z-score of a composite measure (15 tests)	$\beta = 0.013$ ($p=0.05$)	Age, sex, education, race

Tangney et al. 2011 USA ⁸⁹	N=3790 Age ≥65 Sex (F) 62% Community	7.6	139 item-FFQ (energy-adjusted)	MedDietScore (0-55) (veg, legumes, fruits, olive oil, potatoes, fish, non-refined cereals, meat, poultry, full-fat dairy, alcohol) MedDiet wine (wine as alcohol drink) HEI-2005 (0-100) (whole fruits, veg, dark green and orange veg and legumes, total grains, whole grains, milk, meat and beans, oils, sodium, %E from solid fat, sugar, alcohol)	Z-scores of 4 tests MMSE and some domains	3 rd tertile of MedDietScore: $\beta=0.017$ ($p<0.001$) MedDiet wine: $\beta=0.01$ ($p<0.05$) HEI-2005: $\beta=0.006$ ($p=0.194$)	Age, sex, education, energy intake, race, participation in cognitive activities
Shatenstein et al. 2012 Canada ⁹⁰	N=1488 Age ≥67 Sex (F) 53% Community	3	78 item-FFQ	C-HEI (0-100) (grains, veg/fruit, milk, meat, other, %E from total fat, %E from saturated fat, sodium, cholesterol)	3MS (modified MMSE)	No significant associations	Age, sex, education, income, alcohol, waist circumference, functional status, supplement use, depression
Cherbuin et al. 2012 Australia ⁹¹	N=1528 Age 60-64 Sex (F) 51% Community	4	215 item-FFQ	MeDi (0-9) (veg, legumes, fruits and nuts, cereals, fish, meat, dairy, MUFA/SFA, alcohol).	Z-score of 5 domains tests	No significant associations	Age, sex, education, BMI, APOE ε4, energy intake, exercise, diabetes, CVD
Vercambre et al. 2012 USA ⁹²	N=2054 Age ≥65 Sex (F) 100% With vascular disease	5.4	116 item-FFQ	MeDi (0-9) (veg, legumes, fruits, cereals, fish, meat, dairy, MUFA/SFA, alcohol)	Global cognition and some domains	No significant associations	Age, education, BMI, energy intake, marital status, exercise, diabetes, CVD, vitamins & drug use, depression
Titova et al. 2013 Sweden ⁹³	N=194 Age ≥70 Sex (F) 48% Community	5	7-day food diary (energy-adjusted)	MeDi (0-8) (veg and legumes, fruits, cereals and potatoes, fish, meat, dairy, PUFA/SFA, alcohol)	7-minutes screen (7MS)	No significant associations	Sex, education, BMI, energy intake, physical activity, LDL, SBP, diabetes
Samieri et al. 2013 USA ⁹⁴	N=16058 Age ≥70 Sex (F) 100% Stroke-free	13	116 item-FFQ	Alternative MeDi (0-9) (veg excluding potatoes, fruits, nuts, whole grains, legumes, fish, red meat, MUFA/SFA, alcohol)	Tele-MMSE and some domains	No significant associations	Age, education, BMI, energy intake, lifestyle, CVD, diabetes, vitamin use, depression

Wengreen et al. 2013 USA ⁹⁵	N=3580 Age ≥65 Sex (F) 57% Community	11	142 item-FFQ (energy-adjusted)	DASH (fruit, veg, low-fat dairy, nuts and legumes, whole grains, sodium, sweetened beverages, red meat) Mediterranean diet (fruit, veg, grains, fish, legumes, MUFA/SFA, meat, high-fat dairy)	3MS (0-100)	No significant associations for each index	Age, sex, education, BMI, lifestyle, diabetes, CVD, supplement use
Samieri et al. 2013 USA ⁹⁶	N=6174 Age ≥65; Sex (F) 100% Nurses	5	131 item-FFQ	Alternative MeDi (0-9) (veg excluding potatoes, fruits, nuts, whole grains, legumes, fish, red meat, MUFA/SFA, alcohol)	Tele-MMSE and some domains	No significant associations	Age, education, BMI, energy intake, lifestyle, CVD, diabetes, vitamin use, depression
Parrott et al. 2013 Canada ⁹⁷	N=1099 Age ≥68 Sex (F) 50% Community	3	78 item-FFQ	2 factors: Prudent pattern (veg, fruits, fatty fish, low-fat dairy, poultry, legumes) Western pattern (beef, potatoes, white bread, baked goods, processed meat, high-fat dairy, salty snacks)	3MS	$\beta_{\text{prudent}}=0.25$ ($p<0.01$) $\beta_{\text{Westren}}=-0.23$ ($p<0.01$) in subgroups	Age, sex, education, BMI, energy intake, lifestyle, SES, diabetes, CVD, supplement & drug use, depression
Tsivgoulis et al. 2013 USA ⁹⁸	N=17478 Age ≥45; Sex (F) 57% Community	4	109 item-FFQ (energy-adjusted)	MeD (0-9) (veg, fruits, cereals, legumes, fish, meat, dairy, MUFA/SFA, alcohol)	Cognitive impairment as SIS (0-6) decline to ≤4	OR=0.87 (0.76-1.00) ($p=0.046$)	Age, sex, education, BMI, race, lifestyle, income, diabetes, CVD, supplement & drug use
Gardener et al. 2014 USA ⁹⁹	N=527 Age ≥60 Sex (F) 60% Volunteers	3	101 item-FFQ (energy-adjusted)	AusMeDi (0-9) (fruit, veg, legumes, cereals, fish, meat, dairy, MUFA/SFA, alcohol) 2 factors: Western and prudent patterns	Z-scores of 6 domain tests	No significant associations, but in some subgroups	Age, sex, education, BMI, energy intake, smoking, CVD, diabetes

Tangney et al. 2014 USA ¹⁰⁰	N=826 Age ≥65 Sex (F) 73% Community	4.1	144 item-FFQ (energy-adjusted)	MedDietScore (0-55) (veg, legumes, fruits, olive oil, potatoes, fish, non-refined grains, meat, poultry, full-fat dairy, alcohol) DASH (0-10) (total grains, fruit, veg, dairy, nuts, legumes, meat, poultry, fish, %E from total fat, %E from saturated fat, sweets, sodium)	Z-scores of 19 tests, and some domains	3 rd tertiles: MedDietscore $\beta=0.034$ ($p=0.003$) DASH $\beta=0.022$ ($p=0.04$)	Age, sex, education, energy intake, participation in cognitive activities
Koyama et al. 2014 USA ¹⁰¹	N=2326 Age 70-79 Sex (F) 51% Community	8	108 item-FFQ	MedDietScore (0-55) (veg, legumes, fruits, olive oil, potatoes, fish, non-refined grains, meat, poultry, full-fat dairy, alcohol)	3MS	3 rd tertile: $\beta=0.22$ ($p=0.01$) in blacks	Age, sex, education, BMI, energy intake, SES, lifestyle, diabetes, depression
Galbete et al. 2015 Spain ¹⁰²	N=823 Age >55 Sex (F) 29% Uni. graduates	2	136 item-FFQ	MeDi (0-9) (veg, legumes, fruits, cereals, fish, meat, dairy, MUFA/SFA, alcohol)	TICS-m (5 domains)	Low+moderate vs. high $\beta=-0.056$ ($p=0.011$)	Age, sex, education, BMI, APOE $\epsilon 4$, energy intake, lifestyle, diabetes, CVD
Olsson et al. 2015 Sweden ¹⁰³	N=1038 Age 70 No women Community	12	A 7-day food record (energy-adjusted)	HDI (modified) (-1 to 8) (fruit and veg, fish, %E from total carbohydrate, fiber, %E from sucrose, %E from protein, %E from PUFA, %E from SFA, cholesterol) mMDS (0-8) (veg and legumes, fruits and berries, cereals and potatoes, fish, meat, dairy, PUFA/SFA, alcohol) LCHP (2-20) (total carbohydrate, total protein)	MMSE	No significant associations	Education, APOE $\epsilon 4$, energy intake, lifestyle, living alone
Morris et al. 2015 USA ¹⁰⁴	N=960 Age 81 (mean) Sex (F) 75% Retirement communities	~5	144 item-FFQ	MIND (0-15) (green leafy veg, other veg, berries, nuts, olive oil, butter/margarine, cheese, whole grains, fish, beans, poultry, meat, fast foods, pastries & sweets, wine)	Z-scores of 19 tests, and some domains	MIND: $\beta=0.01$ ($p<0.001$)	Age, sex, education, APOE $\epsilon 4$, energy intake, lifestyle, CVD, diabetes, participation in cognitive activities

Trichopoulou et al. 2015 Greece ¹⁰⁵	N=401 Age ≥65 Sex (F) 64% Volunteer	~7	150 item- FFQ	Traditional Greek MD (0-9) (veg, legumes, fruits and nuts, cereal, fish, meat, dairy, MUFA/SFA, alcohol)	MMSE Changes as: Mild decline (1-4 points) Substantial decline (≥5)	Mild decline: OR=0.46 (0.25 to 0.87) Sub. decline: OR=0.34 (0.13 to 0.89)	Age, sex, education, BMI, energy intake, lifestyle, diabetes, CVD, cohabiting
Smyth et al. 2015 Canada ¹⁰⁶	N=27860 Age ≥55 Sex (F) 29% From two trials	~5	20 item- FFQ	mAHEI (0-70) (veg, fruits, nuts and soy proteins, whole grains, deep-fried foods, ratio of fish to meat and egg, alcohol)	MMSE decrease ≥3	5 th quintile of mAHEI HR= 0.76 (0.66 to 0.86)	Age, sex, education, BMI, lifestyle, CVD, diabetes, depression, drug use, certain biomarkers, region
Männikkö et al. 2015 Finland ¹⁰⁷	N=1140 Age 57-78 Sex (F) 50% Community	4	A 4-day food record	Nordic diet score (modified) (0-22) (fish, veg including legumes & nuts but no potatoes, fruits & berries, whole grain bread, meat & poultry, alcohol, α-linolenic acid, unsaturated fat/total fat)	CERAD-TS (0-100) MMSE	No significant associations	Age, sex, education, energy intake, smoking, drug use, VO _{2max}
Granic et al. 2016 UK ¹⁰⁸	N=791 Age 85 Sex (F) 62% Community	5	24-hour dietary recalls on 2 days	3 clusters: - High red meat - Low meat - High butter	SMMSE (0-30) and some domains	No significant associations	Sex, education, BMI, APOE ε4, marital status, lifestyle, multimorbidity

Abbreviations: **ADL**= activities of daily living, **APOE**= apolipoprotein E; **AusMeDi**= Australian-style Mediterranean diet, **BMI**= body mass index; **CERAD-TS**= Consortium to Establish a Registry for Alzheimer's Disease-Total Score, **C-HEI**= Canadian Healthy Eating Index, **CVD**= cardiovascular disease, **DASH**= Dietary Approaches to Stop Hypertension, **FFQ**= Food Frequency Questionnaire, **HDI**= Healthy Diet Indicator, **HEI**= Healthy Eating Index, **LCHP**= Low-Carbohydrate High-Protein score, **LDL**= low-density lipoprotein cholesterol, **mAHEI**= modified Alternative Healthy Eating Index, **MD**= Mediterranean Diet, **MeD**= Mediterranean Diet, **MeDi**= Mediterranean Diet, **MedDietScore**= Mediterranean Diet Score, **MIND**= Mediterranean-DASH Intervention for Neurodegenerative Delay, **mMDS**= modified- Mediterranean Diet Score, **MMSE**= Mini-Mental State Examination, **MUFA/SFA**= ratio between mono-unsaturated fatty acids and saturated fatty acids, **N**= number; **PUFA/SFA**= ratio between poly-unsaturated fatty acids and saturated fatty acids, **RFS**= Recommended Food Score, **SBP**= systolic blood pressure, **SES**= socioeconomic status, **SIS**= Six-Item Screener, **SMMSE**= Standardized Mini-Mental State Examination, **Tele-MMSE**= telephone-based assessment of MMSE, **TICS-m**= modified Telephone Interview for Cognitive Status, **VO2max**= maximum rate of oxygen consumption (as an indicator of overall level of cardiovascular and respiratory fitness), **3MS**= A expanded (modified) version of MMSE, **%E**= Percent of energy.

2 AIMS

2.1 GENERAL AIM

The general aim of this thesis is to investigate the impact of nutrition and diet on cognitive decline and survival in the older population.

2.2 SPECIFIC AIMS

The specific aims addressed in four studies are summarized below.

1. To investigate the prevalence of malnutrition and risk for malnutrition, and to examine the impact of these factors on survival in older people, taking nutritional and inflammatory biomarkers into account (Study *I*).
2. To identify dietary patterns in a ≥ 60 year old population, to investigate the individual impact of different dietary patterns on cognitive decline, and also to explore the combined effect of mixed dietary pattern on changes in cognitive function (Study *II*).
3. To identify a dietary pattern index associated with lower levels of cognitive decline in a Nordic population and compare this association with the association between other dietary indices and cognitive decline (Study *III*).
4. To examine the combined effect of healthy diet and leisure activities, including physical, mental and social dimensions, on cognitive decline over time and to assess the extent to which an active lifestyle reinforces the protective effect of a healthy diet on cognitive decline (Study *IV*).

3 MATERIAL AND METHODS

All four studies used data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K).



3.1 SNAC-K POPULATION

The SNAC-K is a community-based longitudinal study that is conducted in the Kungsholmen area of central Stockholm, Sweden, and was launched in 2001.¹⁰⁹ SNAC-K participants are a random sample of people aged ≥ 60 years living either at home or in institutions. The sampling is stratified by age cohort and year of assessment. In 2001, a total of 11 age cohorts were chosen with six-year intervals between the younger cohorts (60, 66, and 72 years) and three-year intervals between the older cohorts (78, 81, 84, 87, 90, 93, 96 and 99+ years). A total of 5111 people were initially selected for participation; of those, 200 died before start of the study, 262 had no contact information, 32 had moved, 23 did not speak Swedish, and four were deaf. At baseline (2001 to 2004; T1), 73.3% (response rate) of the 4590 people who were alive and eligible to participate were examined. Home visits (n=717) were conducted with those who agreed to participate but were unwilling or unable to come to our research centre.

The study sample for this PhD project was derived from participants in the SNAC-K baseline assessment; the second wave (April 2004 to June 2007; T2), which includes the examinations of the older cohort; and the third wave (July 2007 to October 2010; T3), which includes the second follow-up of the older cohort and the first follow-up of the younger cohort. After excluding people with dementia (n=311) or missing data on dementia (n=10), people without dementia whose Mini-Mental State Examination (MMSE) score was <27 (n=306) or whose MMSE score was missing (n=5), and those with $>20\%$ missing data on the semi-quantitative food frequency questionnaire (SFFQ; n=508), 2223 individuals were left in the current PhD project (**Figure 4**).

Data collection. At baseline and each follow-up, physicians clinically examined all participants in accordance with a standard protocol (available at <http://www.snac.org>; and <http://www.snac-k.se>). Trained personnel administered psychological tests, and nurses collected data on social and personal history.^{109, 110} If the participant was not able to answer, an informant was interviewed, usually the participant's next of kin.

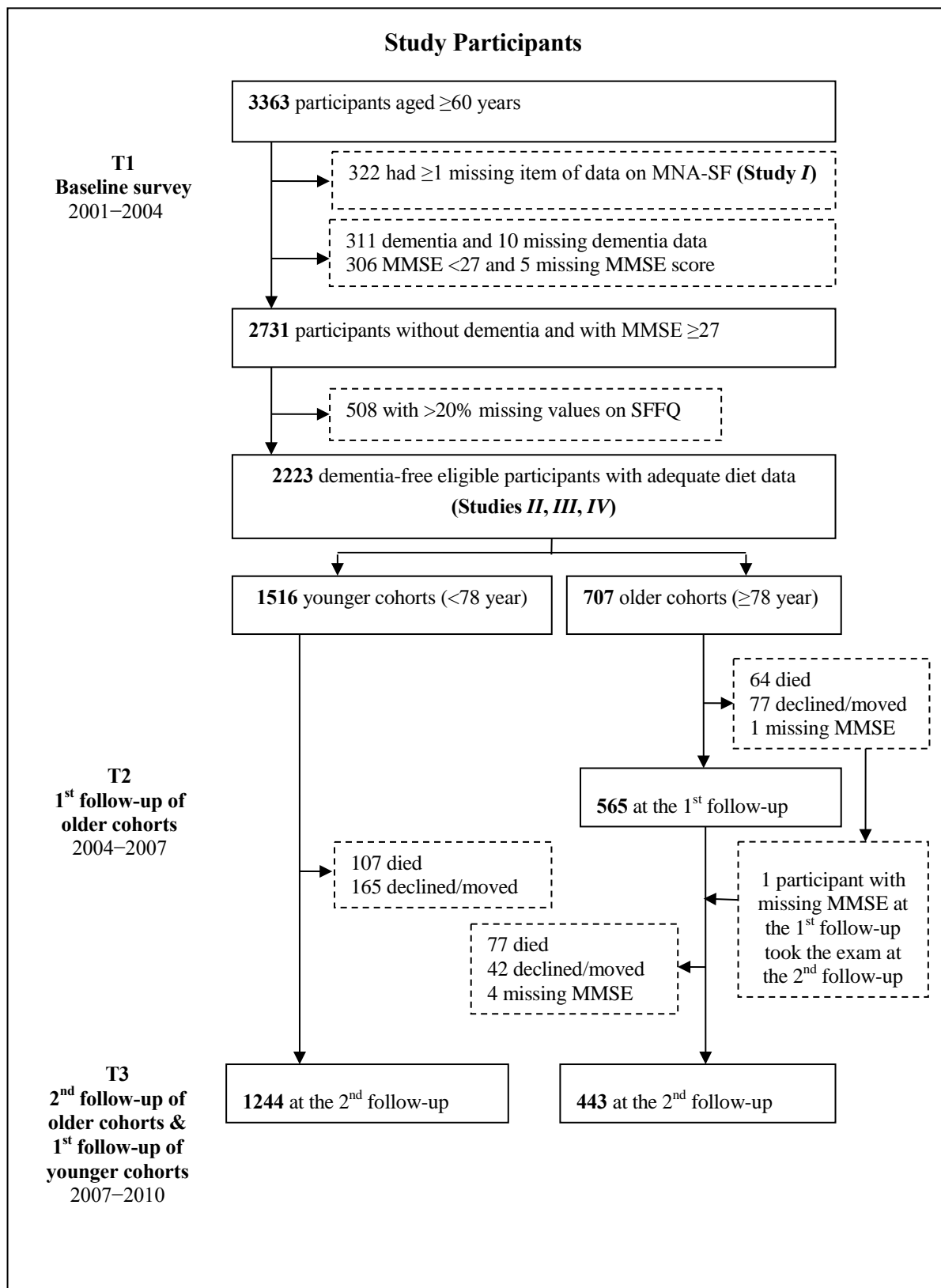


Figure 4. Flowchart of the study population in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), and origins of the study samples in the four studies.

MMSE=Mini-Mental State Examination, SFFQ=semi-quantitative food frequency questionnaire.

3.2 EXPOSURE ASSESSMENT

3.2.1 Nutritional status assessment (Study I)

Nutritional status at baseline was assessed in all participants using the data on components of the Mini-Nutritional Assessment-Short Form (MNA-SF).¹⁷ Data on participants' food intake decline due to loss of appetite and eating difficulties (score 0 to 2), unintentional weight loss (score 0 to 3), mobility (score 0 to 2), stress or acute disease state (score 0 or 2), dementia or depression (score 0 to 2), and body mass index (BMI) (score 0 to 3) was used to screen people for risk of compromised nutritional status.

To more accurately evaluate the mobility status, *functional abilities* were assessed by nurses using the Katz index of ADL, which is a scale to assess dependency in the following six activities: bathing, dressing, toileting, transferring, continence and feeding.¹¹¹ The “*transferring*” item in the ADL was taken into account in scoring the mobility component of the MNA-SF. BMI was computed as the ratio of weight in kilograms to the square of height in meters [$\text{weight}/(\text{height in meters})^2$], using nurse measurements. The BMI cut-offs were ≥ 23 for the full score, and < 19 for zero score.¹⁷ The total MNA-SF score has a range between zero and 14. On the basis of the MNA-SF score, *nutritional status* was categorized as normal (score ≥ 12), risk for malnutrition (score 8–11), or malnutrition (score < 8).

3.2.2 Nutritional and inflammatory biomarker measures (Study I)

Blood samples were taken from the participants at baseline for laboratory tests. Haemoglobin (Hb) was measured using the sodium lauryl sulphate method (Sysmex XE-5000, Sysmex Corp., Kobe, Japan); serum Alb was measured by the bromcresol purple dye method (DXC800, Beckman Coulter, Brea, CA, USA); and CRP was measured by a turbidimetric method (DXC800, Beckman Coulter). In accordance with WHO criteria, Hb concentrations < 130 g/l in men and < 120 g/l in women were used to diagnose anaemia.²⁵ Hypoalbuminemia was defined as Alb concentrations of < 37 g/l.¹¹² CRP was divided into three levels on the basis of its distribution: normal (0–5 mg/l, lab reference value), high (6–20 mg/l), and very high (> 20 mg/l).

3.2.3 Dietary assessment (Studies II–IV)

A validated, self-administered 98-item SFFQ was used at baseline to assess habitual dietary intake in the study population.¹¹³ Nine different frequencies of consumption allocated to each food item, ranging from “never” to “four times or more per day”. Colour photographs of four plates with increasing portion sizes of staple foods, meat, and vegetables were used to indicate the portion sizes. The national food composition database was used to calculate daily energy and nutrients intake by multiplying frequencies of intake by the relevant portion size values, using the MATs software (Rudans Lättdata, Sweden).¹¹⁴ None of the participants reported an implausible value of total energy intake, when this value was defined as within ± 3 standard deviations of the sex-specific mean of the log-transformed energy intake. The daily frequencies of intake for each food group were adjusted for total energy intake using the

residual approach.¹¹⁵ Misreporting of energy intake was assessed by comparing the reported energy intakes with age- and sex-specific estimates of energy expenditures using the Oxford equation by Henry.¹¹⁶ Although all misreports were excluded in sensitivity analyses, under-eaters were differentiated from under-reporters by assessing participants' reported recent involuntary weight loss (undereating was more likely in those with >20% weight loss).¹¹⁷

3.2.4 Active lifestyle assessment (Study IV)

Leisure activities were assessed by asking the participants whether they had regularly engaged in any particular activities or belonged to any organizations during the last 12 months. If they answered yes, they were asked to specify the types of activities or organizations and to report the frequency of participation. The reported activities were grouped into mental, physical, and social pursuits that were performed at least once a week outside work-related activities; we rated the level of activity as in a previous study.^{118, 119}

Physical activity level was defined as: 1) "intense" if the study participant reported taking part in intense physical exercise (e.g. brisk walking, jogging, long bike rides, intense gym exercise, or other sports) at least once a week; 2) "moderate" if the participant reported doing moderate physical exercise (e.g. walking, short bike rides, light gym exercises, or golf) or other physical activities, such as gardening, picking mushrooms/berries, hunting/fishing, home repairs, and mechanical work on their car at least once a week; and 3) "low" if the participant reported performing the aforementioned physical exercise/activities less than once a week.

Mental activities consisted of reading newspapers/magazines, reading books, playing chess, playing an instrument, listening to music, using the Internet/a computer, and painting/drawing. Mental activity level was categorized as: 1) "intense" if the study participant engaged in >3 activities/week; 2) "moderate" if the study participant engaged in 2–3 activities/week; and 3) "low" if the participant engaged in ≤1 activity/week.

Social activities included going to the movies, going to the theatre, attending concerts, visiting museums/art exhibitions, attending sports events, going to restaurants/pubs/cafes, playing bingo, dancing, attending religious activities, attending courses, travelling, attending social meetings, and doing voluntary work. It was categorized as: 1) "intense" if the study participant reported engaging in >1 of the activities/week; 2) "moderate" if the participant engaged in 1 of the activities/week; and 3) "low" if the person engaged in none of the activities/week.

An active lifestyle. On the basis of the levels of participation in three dimensions of activity, *total leisure activity* was scored as "0" if participation in at least two of the three dimensions of activity was low and the third one was low/moderate, "1" if two of the dimensions were moderate and the third was moderate/intense, and "2" if at least two of the dimensions were intense. The person was categorized as having an *active lifestyle* if the leisure activity score was ≥1. Those with a leisure activity score of 0 were classified as having an inactive lifestyle.

3.3 OUTCOME ASSESSMENT

3.3.1 Assessment of survival status (Study I)

Information about the survival status of the participants was derived from the Swedish Cause of Death Register at the National Board of Health and Welfare. Information until 15 October 2012 was used in this thesis. Approximately 93% of all deaths in Sweden are reported within 10 days, and 100% are reported within 30 days.¹²⁰

3.3.2 Dementia diagnosis at baseline (Studies I–IV)

A validated 3-step procedure was used to diagnose prevalent dementia and various types of dementia at baseline.¹²¹ Through a structured interview, clinical examination, and cognitive evaluation, the examining physician made the preliminary diagnosis on the basis of the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R).¹²² All preliminary diagnoses of dementia were reviewed by a second physician, and a third opinion was solicited in case of disagreement.

3.3.3 Global cognitive function (Studies II–IV)

To assess the global cognition, the MMSE was administered at baseline and at first and second follow-ups. The MMSE is a 30-point questionnaire that includes questions about different cognitive functions such as orientation to time and place, attention and calculation, recall, language, ability to follow written and verbal commands, and visual construction.⁴⁶ The most commonly used MMSE cut-off in clinical settings for dementia diagnosis is ≤ 24 .¹²³ However, mild cognitive dysfunction might be present in those with high educational level and an MMSE score of < 27 .¹²⁴

3.4 COVARIATES

Assessment of socio-demographic characteristics and other lifestyle factors.

Demographic data (e.g. *age*, *sex*, and *education*) was collected during the nurse interviews. *Educational level* was measured as the total years of formal schooling. The variable was further divided into three main categories: elementary school (< 8 years), high school (8–13 years), and university (≥ 14 years).¹¹⁰ *Living arrangements* were categorized as living at home with someone, living at home alone, or living in an institution. *Civil status* was defined as married (which included those who were cohabiting), single, and widow/divorced.

Smoking was assessed by asking participants whether they had ever smoked. Current and former smokers were asked how long they had been smokers or how long they had smoked. We categorized participants as ever-smokers or never-smokers.

Physical activity was initially assessed on the basis of WHO and American College of Sports Medicine recommendations and was categorized as 1) inadequate: never, < 2 –3 times/month, or 2–3 times/month; 2) health-enhancing: light exercise several times/week or every day; and 3) fitness-enhancing: moderate to intense exercise several times/week or every day.¹²⁵

Social networks variable was defined on the basis of participants' marital status, living arrangements, parenthood, friendships, and frequency of and satisfaction with social contacts. Participants were grouped into the three social network categories: rich, moderate, and limited or poor.^{118, 126} The rich social network category included those who were married and lived with someone, had children, relatives, or friends with whom they were in daily to weekly contact, and found this level of contact satisfactory. The moderate social network category included those who had any two of the three elements. The limited or poor social network category included those who had one or none of the three elements.

Chronic disease and biomarkers. A disease was classified as chronic if one or more of the following characteristics were present: 1) the disease was permanent, 2) it was caused by non-reversible pathological alteration, 3) it required rehabilitation, or 4) it required a long period of care.¹²⁶ *Chronic disorders* were diagnosed by the examining physician on the basis of clinical examination, medical history, laboratory data, and current use of medications. The participants were asked by physicians to show prescription forms and/or the containers for the drugs they used. Drugs were classified on the basis of the Anatomical Therapeutic Chemical (ATC) classification system (e.g. lipid modifying agents: C10; dietary vitamin/minerals supplements: A11 and A12) (<http://www.whocc.no/>). The 9th and 10th revisions of the International Classification of Diseases (ICD-9 and ICD-10) were used for the diagnosis of vascular disorders, including heart disease (i.e. coronary heart diseases [ICD-9 codes 410-414; ICD-10 codes I20-I25]; atrial fibrillation [ICD-9 code 427.8; ICD-10 code I48]; and heart failure [ICD-9 code 428; ICD-10 code I50], and cerebrovascular disease [ICD-9 codes 430-438; ICD-10 codes I60-I69]); cancer (ICD-9 code 140-239; ICD-10 code C00-D49); and depression (ICD-9 code 311; ICD-10 code F32).

Hypertension was defined as systolic/diastolic blood pressure of $\geq 140/90$ mmHg or the use of antihypertensive medications (ATC codes C02, C03, and C07).¹²⁷ Diabetes was diagnosed on the basis of medical history, data from the inpatient registry (ICD-9 code 250; ICD-10 code E11), use of hypoglycaemic medications (ATC code A10), or glycated haemoglobin (HbA1c) $>6.4\%$ (46 mmol/mol).^{128, 129} In accordance with the National Glycohemoglobin Standardization Program, 1.1% was added to the HbA1c value to equate them to international values.¹³⁰ Hypercholesterolemia was defined as non-fasting total plasma cholesterol of ≥ 6.22 mmol/L (≥ 240 mg/dL) or use of lipid-lowering medication (ATC code C10).¹³¹ Genomic DNA was also extracted from peripheral blood samples at baseline, and a standard polymerase chain reaction was used for various genotyping, including Apolipoprotein E (*APOE*) (rs429358).¹³²

3.5 STATISTICAL ANALYSES

The main aims of this doctoral thesis were achieved by carrying out a set of different analyses in each study. The youngest (60–66 years old) and the oldest (≥ 90 years) age groups in SNAC-K were oversampled at baseline. Thus, the sampling weight method with age group stratification was used to weight each age group sample back to the original population from

which the samples were drawn. The number of people in each age strata in the original population was divided by the number of people in the corresponding age strata in the study sample to create a weighted variable. This probability weight was used in the analyses. To present baseline characteristics of the cohort, univariate analyses were performed with Chi-square or Fisher's exact tests for categorical variables, and Mann-Whitney test, analysis of variance with post hoc comparison using the Bonferroni test, or quantile regression for continuous variables. Potential statistical interactions between covariates, including the independent variables and their cross-product terms were assessed in the same statistical models. The likelihood ratio test was used to test the statistical interactions.

Imputation of missing data. Large-scale epidemiological studies, especially those that use long questionnaires or collect data longitudinally, inevitably have to deal with the problem of non-response that creates missing values. Missing data in the predictor variables can lead to bias in the risk estimates and loss of statistical power.^{133, 134} Missing data can be handled either by use of the traditional deletion techniques (i.e. complete-case analysis) or imputation techniques (i.e. filling in the missing values).¹³⁴ Complete-case analysis has long been criticized for leading to loss of information and thus analytical power and for causing bias in estimates and inferences, especially when systematic differences between observed and unobserved values are related to a specific exposure-outcome association.^{135, 136}

Multiple imputation techniques have been proposed as a valid alternative. In this doctoral project, multiple imputation by chained equation (MICE)¹³³ was used to replace missing values in the SFFQ; at least 10 completed datasets were generated. The results obtained from multivariable regression models estimated on the basis of the imputed dataset were then combined using Rubin's rule to produce overall estimates and standard errors that reflect missing-data uncertainty.¹³⁷ Age, sex, education, civil status, BMI, physical activity, smoking, vascular and other chronic diseases, MMSE score, dietary supplement use, and *APOE* ϵ 4 were considered major covariates in data analyses and in the multiple imputation. All data analyses for the four studies were performed using the imputed data.

The statistical tests were 2-sided and considered statistically significant at *P*-values of <0.05 . Statistical analyses for all studies were performed and graphs created with Stata®, version 12 or later (StataCorp, TX, USA). The following specific statistical procedures were applied in each of the four studies (**Table 4**):

Study I

The associations between sociodemographic and biomarker (Hb, Alb, and CRP) measures and nutritional status (MNA-SF categories) were assessed with multinomial logistic regression (those with normal nutritional status were used as the reference group).

Hazard ratios (HR) and 95% confidence intervals (CI) for the associations between nutritional status and mortality rates were estimated by applying flexible parametric survival models. Additionally, the associations between mortality and the combination of nutritional

status and biomarkers (Hb and Alb) were examined using the same models. To add the dimension of time to the association between mortality and the combination of nutritional status and biomarkers, the Laplace regression method was used to model the median survival time.

Sensitivity analyses excluded those who died during the first 3 years of the study; and participants who lived in institutions. Additional sensitivity analysis was performed after imputation of the missing data.

Study II

After grouping the 98 food items into 35 food groups on the basis of similarities in their nutrient contents, we conducted exploratory factor analysis (principle component) to aggregate correlated food variables, and used orthogonal transformation (varimax rotation) for factors rotation. Two dietary patterns were identified and labelled the “Western”, and “prudent” dietary patterns. Four groups of adherence levels to these two dietary patterns were created on the basis of different combination of the quintiles of pattern scores as shown in **Figure 5**.

The associations between dietary patterns, individually and in combination, and MMSE changes were examined with multilevel mixed-effects linear regression. Sensitivity analyses included the assessment of the association between all-cause mortality and each dietary pattern with parametric survival models; exclusion of those with energy misreporting; and the complete case analysis.

		Prudent diet adherence				
		Very low	Low	Moderate	High	Very high
Western diet adherence	Very low	Low protection and Low risk (n=526)			High protection and Low risk (n=366)	
	Low					
	Moderate	Low protection and High risk (n=817)			High protection and High risk (n=514)	
	High					
	Very high					

Figure 5. Joint classification of simultaneous adherence to both Western and prudent dietary patterns.

Those in the dark gray zone were assumed to be at high risk for cognitive decline; those in the light gray zones, at a moderately high risk for cognitive decline; and those in the white zone, at low risk for cognitive decline.

Study III

Construct and analyses of dietary pattern indices: 1) Independent associations between the constituents of the Western and prudent dietary patterns and changes in MMSE scores were assessed with multivariable mixed-effects linear regression. 2) Dietary items that were significantly associated with MMSE change were selected and used to construct the *Nordic*

Prudent Dietary Pattern (NPDP). 3) Mixed-effects linear regression was applied to examine the association between the NPDP and MMSE change.

To compare how well this new index predicts cognitive decline in a Nordic population with how well previously proposed dietary indices predict such decline, we used food items specified in the literature to calculate four predefined healthy dietary indices: *MIND*,¹³⁸ *MedDietScore*,¹³⁹ *DASH*,¹³⁸ and the Baltic Sea Diet (*BSD*).¹⁴⁰

To improve comparability of the results, a harmonized scoring metric was used for all the five dietary indices: 1) Intake of food components in each index was dichotomized using the energy-adjusted and standardized sex-specific population-median of food intake (frequencies/day) as the cut-off to define low and high consumption. 2) For the consumption of food items presumed to be healthy, a score of 0 was assigned to intakes below the median, and scores of 1 to 5 were assigned to quintiles of intakes above the median. For the consumption of food components presumed to be less healthy, the scoring was reversed. 3) For the BSD, alcohol intake was scored as 1 (>0 to 10 grams/day in women, and >0 to 20 grams/day in men) or 0 (all other amounts).¹⁴¹ For other indices, the safe daily intake of wine was defined as >0 to ≤1 drink for women, and >0 to ≤2 drinks for men.¹⁴² 4) The scores assigned to dietary components intake in each index were summed to a total score. A higher score indicated greater adherence to the diet in question.

HRs and 95% CIs of MMSE decline to ≤24 for different levels of adherence to each dietary index were evaluated using parametric survival models. The cumulative hazard function curves for predicting MMSE decline to ≤24 over 6 years were compared in people who had high adherence to each of the diets. The receiver operating characteristic (ROC) curves were used to compare the ability of dietary indices to correctly predict MMSE decline. Sensitivity analyses included complete case analysis, and an analysis that excluded those who misreported their energy intake.

Study IV

Multivariate mixed-effects linear regression models were used to examine the associations between rate of change in MMSE score over 6 years and 1) adherence to the NPDP; 2) each of the physical, mental, and social activities; 3) simultaneous adherence to the NPDP and being engaged in each of the three activity dimensions; 4) simultaneous adherence to the NPDP and being active considering total leisure activity.

Parametric survival models were used to estimate the HRs and 95% CIs of the risk of MMSE decline to ≤24 in relation to the NPDP and activity levels, both independently and in combination. Follow-up time was censored at the date of examination in which MMSE decline to ≤24 was detected, the date of death, or the end of the second follow-up, whichever occurred first. Sensitivity analyses included complete case analysis, and an analysis that excluded those who misreported their energy intake.

Table 4. Outcome, exposures, potential cofounders, and statistical analyses used in the studies included in this thesis

Study	Outcome(s)	Exposures	Potential cofounders	Statistical analyses	Comments
Study I	All-cause mortality over 11 years Difference in median age at death	Nutritional status (MNA-SF) Combined MNA-SF assessment and biomarker levels	Age, sex, education, living arrangement	Parametric survival models Laplace regression	Mortality rates (per 1000 persons-years) were age-, sex- and education-standardized in MNA-SF groups Interactions of age, sex and education with poor nutritional status on mortality
Study II	Change in MMSE scores over 6 years	Population-specific dominant dietary patterns, individually and in combination	Age, sex, education, civil status, smoking, physical activity, BMI, dietary supplement use, vascular and other chronic diseases, APOE ε4, energy intake	Principal component (exploratory factor) analysis Multilevel mixed-effects linear regression Parametric survival models	1 st model: age, sex, education, energy intake 2 nd model: 1 st model + all other covariates Interactions of each covariate with time, and interactions of each covariate with diet over time on MMSE change
Study III	Change in MMSE scores over 6 years Decline in MMSE scores to ≤24 over 6 years	Cognition-specific dietary index (NPDP) Other predefined dietary indices: MIND, MedDietScore, DASH, BSD	Age, sex, education, civil status, smoking, physical activity, BMI, dietary supplement use, vascular and other chronic diseases, APOE ε4, survival status, energy intake, and other dietary items	Multilevel mixed-effects linear regression Parametric survival models Cumulative hazard function curve Receiver operating characteristic (ROC) curves	Inter-correlations between index scores were examined Diet scores were assessed as both continuous and tertiles Reference category was always the low adherence level Interactions test as above
Study IV	Change in MMSE scores over 6 years Decline in MMSE scores to ≤24 over 6 years	Cognition-specific dietary index (NPDP) Physical, mental, and social activities, individually, and in combination as total leisure activity Combined diet and leisure activities	Age, sex, education, civil status, smoking, smoking duration, BMI, dietary supplement use, vascular and other chronic diseases, APOE ε4, survival status, energy intake, and other lifestyle factors	Multilevel mixed-effects linear regression Parametric survival models	1 st model: crude 2 nd model: fully adjusted Reference category was always the low diet adherence and low activity levels Interactions test as above

4 ETHICAL CONSIDERATIONS

All people living in the Kungsholmen district who were aged ≥ 60 years and eligible for the SNAC-K study at baseline (2001-2004), were sent a personal letter. This letter explained the nature of the project and the importance of participation and emphasized that involvement was voluntary. Thereafter, all potential participants were contacted by phone to check their availability and to book a date for their first visit. At the screening evaluation, informed consent was obtained directly from each person, after explaining the aims of the project and clarifying that all information would be kept strictly confidential. If there was any indication that the person had severe cognitive impairment, consent was obtained from a proxy, usually the participant's next of kin or a close relative. The examination or interview was interrupted if the participant, in any way, expressed anguish or discomfort, regardless of whether the participant or a proxy had provided informed consent. All phases of the SNAC-K received approval from the Ethics Committee at Karolinska Institutet, Stockholm, Sweden.

The four studies included in this thesis used the data collected from the baseline to the second follow-up of the project as well as data from medical records, death certificates and the Swedish National Patient Register. For each wave of follow-up data collection, approval from the Ethics Committee at Karolinska Institutet was obtained:

- Baseline survey (2001-2004): Dnr. 01-114
- The first follow-up examination (2004-2007): Dnr. 04-929/3
- The second follow-up examination (2007-2010): Ö 26-2007
- Death and patient register data: Dnr. 2009/595-32

All staff members who work with the SNAC-K database follow the guidelines of the Swedish Council for Research in the Humanities and Social Sciences, including the principles of autonomy and integrity, the rule of consent, and use of research. All researchers working with SNAC-K follow the ethical guidelines and the ethical principles for medical research involving human subjects expressed in the Declaration of Helsinki.

5 RESULTS

5.1 CHARACTERISTICS OF THE STUDY POPULATION

Of the initial 2731 non-demented people with relatively cognitively intact status, 508 were excluded from the diet-cognition studies because >20% of the values on their SFFQ were missing at baseline. Comparison of the remaining group (i.e. respondents) with those excluded (i.e. non-respondents) showed significant demographic and health differences between two groups; however, there was no difference in their baseline MMSE scores (**Table 5**).

In logistic regression analysis, being a non-respondent was associated with older age (≥ 78 y) (OR: 3.59; 95% CI: 2.94 to 4.39), female sex (OR: 1.27; 95% CI: 1.04 to 1.56), a lower level of education (elementary school) (OR: 2.39; 95% CI: 1.85 to 3.09), being single/widow/divorced (OR: 2.04; 95% CI: 1.67 to 2.50), living in an institution (OR: 7.42; 95% CI: 2.68 to 20.51), never having smoked (OR: 0.73; 95% CI: 0.60 to 0.89), low BMI (< 19 kg/m²) (OR: 2.93; 95% CI: 1.82 to 4.72), vascular diseases (OR: 1.73; 95% CI: 1.33 to 2.25), and diabetes (OR: 1.55; 95% CI: 1.26 to 1.89).

Table 5. Characteristics of the cognitively intact participants by semi-quantitative food frequency questionnaire response at baseline (n=2731)

Characteristics	Respondents (n=2223)	Non-respondents* (n=508)	P-value
Age (years), median (IQR)	67 (17.5)	79 (20.9)	<0.001
Female sex, n (%)	1352 (60.8)	337 (66.3)	0.021
Educational level <8 years, n (%)	436 (19.6)	168 (33.3)	<0.001
Single/widow/divorced, n (%)	1084 (48.8)	333 (65.6)	<0.001
Living in an institution, n (%)	6 (0.3)	10 (2.0)	<0.001
Ever smoking, n (%)	1242 (55.9)	244 (48.0)	0.005
MMSE score, median (IQR)	29 (1)	29 (2)	1.000
BMI, median (IQR)	25.5 (4.8)	24.8 (5.4)	0.003
Vascular disorders, n (%)	1708 (76.8)	433 (85.2)	<0.001
Diabetes, n (%)	702 (31.6)	204 (40.2)	<0.001
Cancer, n (%)	160 (7.2)	42 (8.3)	0.406
Depression, n (%)	122 (5.5)	40 (7.9)	0.107
APOE $\epsilon 4$ carrier, n (%)	614 (27.6)	113 (22.2)	<0.001

* Those with >20% missing values on the semi-quantitative food frequency questionnaire.

† Number of people with missing values: 4 for education, 7 for civil status, 18 for ever smoking, 72 for BMI, 3 for vascular disorders, 73 for diabetes, 8 for depression, and 195 for APOE.

5.2 ASSOCIATION BETWEEN NUTRITIONAL STATUS AND SURVIVAL (STUDY I)

Of the 3041 participants at baseline, 51 (1.7%) were assessed as malnourished, and 751 participants (24.7%) were assessed as being at risk for malnutrition. During the 11-year follow-up period (24,575.4 person-years; median per person=9.1 years), 1073 participants (35.3%) died. After adjusting for age, sex, education, and living arrangements, the mortality hazard for people with malnutrition was 1.5-fold higher and the mortality hazard for those at risk for malnutrition was 2.4-fold higher than those with normal nutritional status, respectively (**Figure 6**).

Anemia was associated with 86%, and hypoalbuminemia with 52% increased odds of being at risk for malnutrition than normal haemoglobin and albumin levels, respectively. The odds ratio of being malnourished was 3.35 (95% CI: 1.57 to 7.15) in those with anemia and 3.57 (95% CI: 1.62 to 7.88) in those with low albumin levels. CRP was associated with risk for malnutrition (OR: 2.23; 95% CI: 1.26 to 3.97), or malnutrition (OR: 5.44; 95% CI: 1.77 to 16.77) only when it was very high.

People with malnutrition or at risk for malnutrition and a low level of any biomarker (i.e. haemoglobin and/or albumin) had higher risk of mortality than people with both normal nutritional status and normal levels of biomarkers (**Figure 7**). Those with malnutrition and low biomarker(s) level were 4 years younger at death (median age at death: -4.31, 95% CI: -5.34 to -3.27) and those at risk for malnutrition that had low biomarker(s) level were 2.5 years younger at death (median age at death: -2.49, 95% CI: -3.15 to -1.83) than those with both normal nutritional status and normal levels of biomarkers.

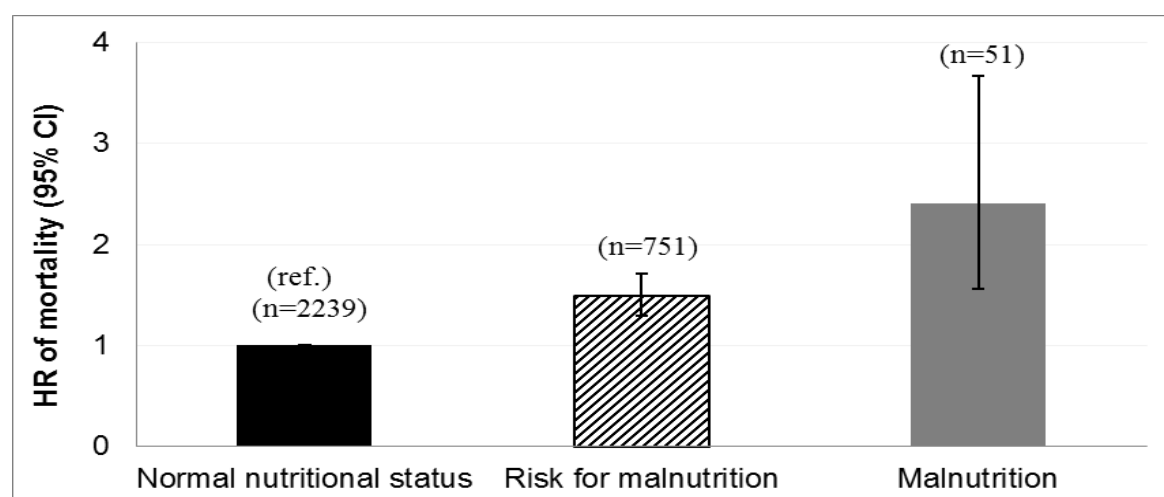


Figure 6. Hazard ratios (HR) and 95% confidence intervals (CI) of 11-year all-cause mortality in relation to nutritional status (defined by MNA-SF). Estimates were adjusted for age, sex, education, and living arrangements.

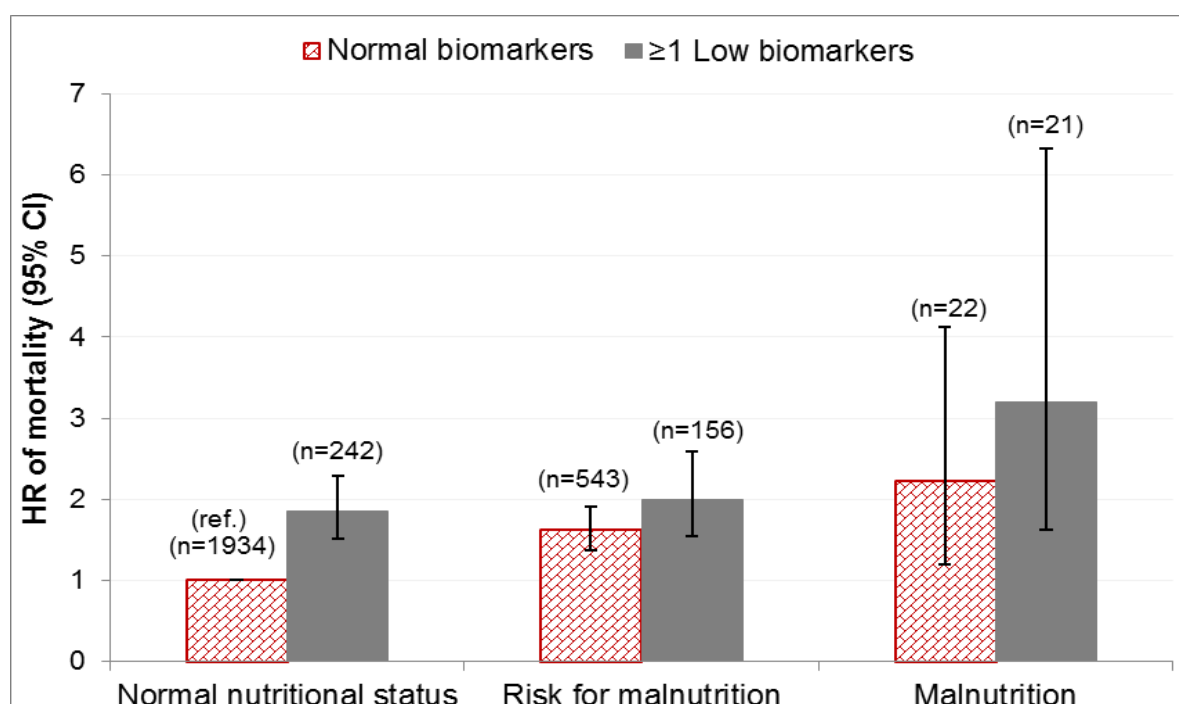


Figure 7. Hazard ratios (HR) and 95% confidence intervals (CI) of 11-year all-cause mortality in relation to joint effect of nutritional status (defined by MNA-SF) and biomarker levels (haemoglobin and albumin).

Biomarker levels were categorized as: normal, or at least one low biomarker level (haemoglobin <130 g/L in men and <120 g/L in women, and/or albumin <37 g/L). Because of the low number of malnourished participants in the very high CRP group (n=5), CRP was not entered in this analysis. Estimates were adjusted for age, sex, education, and living arrangements.

5.3 DIETARY PATTERNS AND COGNITIVE DECLINE (STUDY II)

Of the 2223 participants (mean age 70.6 ± 8.9), 871 (39.2%) were men and 1352 (60.8%) were women. There were 1516 participants (68.2%) in the younger cohorts and 707 (31.8%) in the older cohorts. The Western dietary pattern that we identified was characterized by more frequent intake of fruit juice, potatoes, high-fat spreads and dairy products, butter/margarine, red/processed meat, eggs, refined grains, sugar/sweets/pastries, (salty) snacks, soda, beer and spirits. The prudent dietary pattern that we identified was characterized by more frequent intake of vegetables, fruit, vegetable oil in cooking/dressing, cereals and legumes, whole grains, rice/pasta, fish, low-fat dairy products, poultry, and water. Food items with factor loadings <0.25 (e.g. low-fat spreads, pizza, ice cream, coffee, tea and wine) were assumed to be uncorrelated with either of the two dietary patterns.

After controlling for potential confounders, higher Western dietary pattern scores (i.e. high adherence) were associated with more cognitive decline (β : -0.045, 95% CI: -0.071 to -0.019) than lower scores of this pattern, whereas higher prudent dietary pattern scores were related to less cognitive decline (β : 0.043, 95% CI: 0.017 to 0.068) than lower scores of this pattern.

(Table 7). These results remained significant after adding interaction terms between each dietary pattern score and each covariate in the full-adjusted models.

In the analysis of the combined effect of the Western and prudent patterns on cognitive decline, the best cognitive protection was observed in those who adhered the most to the prudent diet and the least to the Western diet. In contrast, those with high adherence to the Western diet and low adherence to prudent diet had the greatest decline in MMSE scores during follow up (Table 7). A comparison of different levels of adherence to both dietary patterns revealed that higher intakes of prudent dietary components may help counterbalance the negative effects that consuming Western-type dietary items has on cognition.

5.4 NORDIC PRUDENT DIETARY PATTERN (NPDP) AND COGNITIVE DECLINE (STUDY III)

In this study, we first decomposed the two major dietary patterns (prudent and Western) that were identified in Study II into their main food constituents. Then, we examined the independent associations between each food group (and their sub-items) and change in MMSE scores over time. On the basis of the obtained results, we selected 15 food groups/items to construct a new population- and cognition-specific dietary index, the Nordic Prudent Dietary Pattern (NPDP) (Table 6).

Table 6. β -coefficients and 95% confidence intervals (CI) for the associations between constituents of the NPDP index and changes in MMSE scores over 6 years

Dietary groups/items	β^* (95% CI)	P-value
Non-root vegetables	0.039 (0.021 to 0.056)	<0.001
Root vegetables	-0.071 (-0.112 to -0.030)	0.001
Apples/pears/peaches	0.051 (0.006 to 0.096)	0.026
Refined grains/cereals	-0.037 (-0.058 to -0.016)	0.001
Pasta/rice	0.197 (0.089 to 0.306)	<0.001
Poultry	0.456 (0.226 to 0.686)	<0.001
Fish	0.118 (0.013 to 0.223)	0.027
High-fat dairy products	-0.056 (-0.093 to -0.018)	0.004
Butter/margarine	-0.018 (-0.032 to -0.004)	0.014
Vegetable oil	0.068 (0.034 to 0.103)	<0.001
Sugar/sweets/pastries	-0.027 (-0.047 to -0.008)	0.006
Wine	0.123 (0.054 to 0.191)	<0.001
Tea	0.055 (0.024 to 0.085)	0.001
Fruit juice	-0.060 (-0.097 to -0.022)	0.002
Water (plain/mineral)	0.018 (0.001 to 0.035)	0.037

* Adjusted for total energy intake, age, sex, education, civil status, physical activity, smoking, body mass index, vitamin/mineral supplement intake, vascular disorders, diabetes, cancer, APOE ϵ 4, and dietary components other than main exposure(s) in each model.

Dietary constituents of the NPDP, MIND, MedDietScore, DASH, and the BSD are compared in **Appendix 2**. Although all five healthy dietary indices mainly focus on more frequent intake of natural plant-based foods and less frequent intake of saturated/trans fat, there are differences in food classifications. For instance, the NPDP is unique in that it includes non-root vs. root vegetables, specific group of fruits (apples, pears, and peaches), refined grains/cereals, pasta/rice, tea, fruit juice, and water. High adherence to the NPDP was associated with less cognitive decline (β : 0.238; 95% CI: 0.175 to 0.300) than high adherence to MIND, MedDietScore, DASH, and the BSD (**Table 7**). It was also associated with a lower risk of decline to an MMSE score of ≤ 24 (HR: 0.176; 95% CI: 0.080 to 0.386) after adjustment for potential confounders (**Figure 8**).

The ROC curve analysis showed that the NPDP predicted a clinically meaningful decline in global cognitive function better (area under the curve, 0.70) than MIND (0.59), MedDietScore (0.57), and the BSD (0.55).

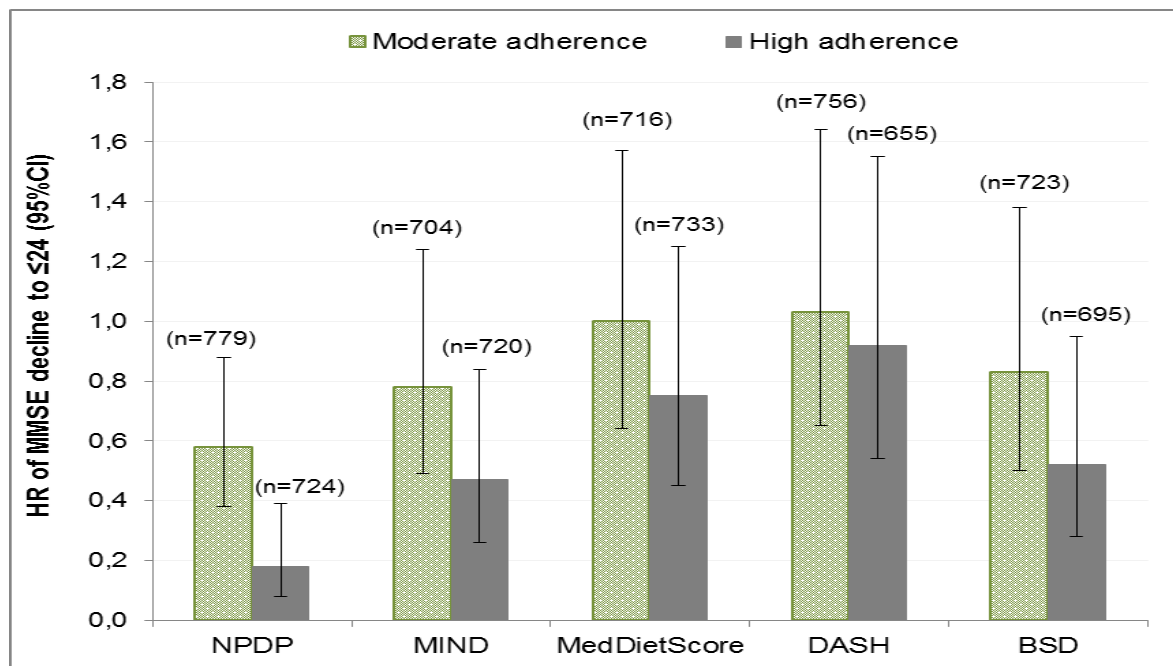


Figure 8. Hazard ratios (HR) and 95% confidence intervals (CI) of decline to an MMSE score of ≤ 24 in relation to adherence levels to five healthy dietary indices. Reference category was the low dietary adherence in each model. Low, moderate, and high adherence levels to each dietary pattern were defined as the first, second, and third tertiles of each total dietary index score, respectively. Estimates were adjusted for total energy intake, age, sex, education, civil status, physical activity, smoking, body mass index, vitamin/mineral supplement intake, vascular disorders, diabetes, cancer, *APOE* $\epsilon 4$, and dietary components other than main exposure(s) in each model.

BSD, Baltic Sea Diet; DASH, Dietary Approaches to Stop Hypertension; MedDietScore, a score that reflects adherence to the Mediterranean diet; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; NPDP, Nordic Prudent Dietary Pattern.

5.5 JOINT EFFECT OF THE NORDIC PRUDENT DIETARY PATTERN AND AN ACTIVE LIFESTYLE ON COGNITIVE DECLINE (STUDY IV)

In mixed-effects models, after adjustment for multiple potential confounders, moderate or high adherence to the NPDP was associated with lower cognitive decline than low adherence. Moreover, moderate or intense physical, mental, and social activities were associated with lower cognitive decline than low activity levels.

Because both moderate and high adherences to the NPDP were related to less cognitive decline, the two categories were merged into one: moderate to high adherence to the NPDP. Similarly, both moderate and intense activity levels (including physical, mental and social dimensions) were associated with lower rates of MMSE change and were combined into a moderate to intense category for each activity in analyses that followed. Furthermore, people with leisure activity scores of “1” and “2” were also grouped together as “ ≥ 1 ” (active lifestyle), because independent of dietary intake and other potential confounders, both had significantly less cognitive decline than those with a leisure activity score of “0” (inactive).

Joint effect analysis showed that an active lifestyle strengthened the protective effect of moderate to high adherence to the NPDP on cognitive function by more than 2-fold (β : 0.33, 95% CI: 0.24 to 0.42 vs. β : 0.16, 95% CI: 0.05 to 0.28) (**Table 7**). In multi-adjusted parametric survival models, moderate to high adherence to the NPDP combined with moderate to intense physical activity, mental or social activity, was associated with additional reduction of risk of a decline to an MMSE score of ≤ 24 than the reference group (low adherence to NPDP and low activity levels). An active lifestyle may significantly strengthen the protective effect of moderate to high adherence to the NPDP against a decline to an MMSE score of ≤ 24 (**Figure 9**).

Table 7. β -coefficients with 95% confidence intervals (CI) for the association of dietary patterns and an active lifestyle with annual rate of change in Mini-Mental State Examination (MMSE) scores

Studies	No. of people	β^* (95% CI)	P-value
Study II	2223		
Western pattern			
1 st quintile \times time	441	Reference	
2 nd quintile \times time	451	-0.08 (-0.15 to 0.004)	0.062
3 rd quintile \times time	441	-0.14 (-0.22 to -0.06)	0.001
4 th quintile \times time	455	-0.06 (-0.14 to 0.02)	0.123
5 th quintile \times time	435	-0.16 (-0.24 to -0.07)	<0.001
Prudent pattern			
1 st quintile \times time	439	Reference	
2 nd quintile \times time	460	0.001 (-0.09 to 0.08)	0.985
3 rd quintile \times time	444	0.06 (-0.02 to 0.14)	0.153
4 th quintile \times time	451	0.12 (0.04 to 0.20)	0.004
5 th quintile \times time	429	0.11 (0.02 to 0.19)	0.011
High prudent & low Western	366	Reference	
High prudent & high Western	514	-0.07 (-0.14 to 0.01)	0.104
Low prudent & low Western	526	-0.08 (-0.16 to 0.001)	0.053
Low prudent & high Western	817	-0.16 (-0.23 to -0.08)	<0.001
Study III	2223		
Moderate/high NPDP	1503	0.19 (0.13 to 0.24)	<0.001
Moderate/high MIND	1424	0.10 (0.05 to 0.15)	<0.001
Moderate/high MedDietScore	1449	0.08 (0.03 to 0.14)	0.005
Moderate/high DASH	1411	0.02 (-0.04 to 0.08)	0.525
Moderate/high BSD	1418	0.04 (-0.02 to 0.09)	0.245
Study IV[†]	2223		
Low NPDP + inactive lifestyle	275	Reference	
Low NPDP + active lifestyle	445	0.17 (0.06 to 0.28)	0.003
Moderate/high NPDP + inactive lifestyle	339	0.16 (0.05 to 0.28)	0.006
Moderate/high NPDP + active lifestyle	1164	0.33 (0.24 to 0.42)	<0.001

* β -coefficients are interactions with time after adjustment for age, sex, education, civil status, total energy intake, dietary vitamin/mineral supplement use, smoking, body mass index, vascular disorders, diabetes, cancer, depression, APOE ϵ 4, survival status, and physical, mental and social activities when applicable. Positive coefficients indicate less and negative coefficients more decline in MMSE scores than in the reference group.

[†] "Low NPDP" refers to low adherence to the NPDP. "Active lifestyle" refers to a leisure-activity score of ≥ 1 . "Inactive lifestyle" refers to a leisure-activity score of 0.

BSD, Baltic Sea Diet; DASH, Dietary Approaches to Stop Hypertension; MedDietScore, Mediterranean Diet Score; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; NPDP, Nordic Prudent Dietary Pattern.

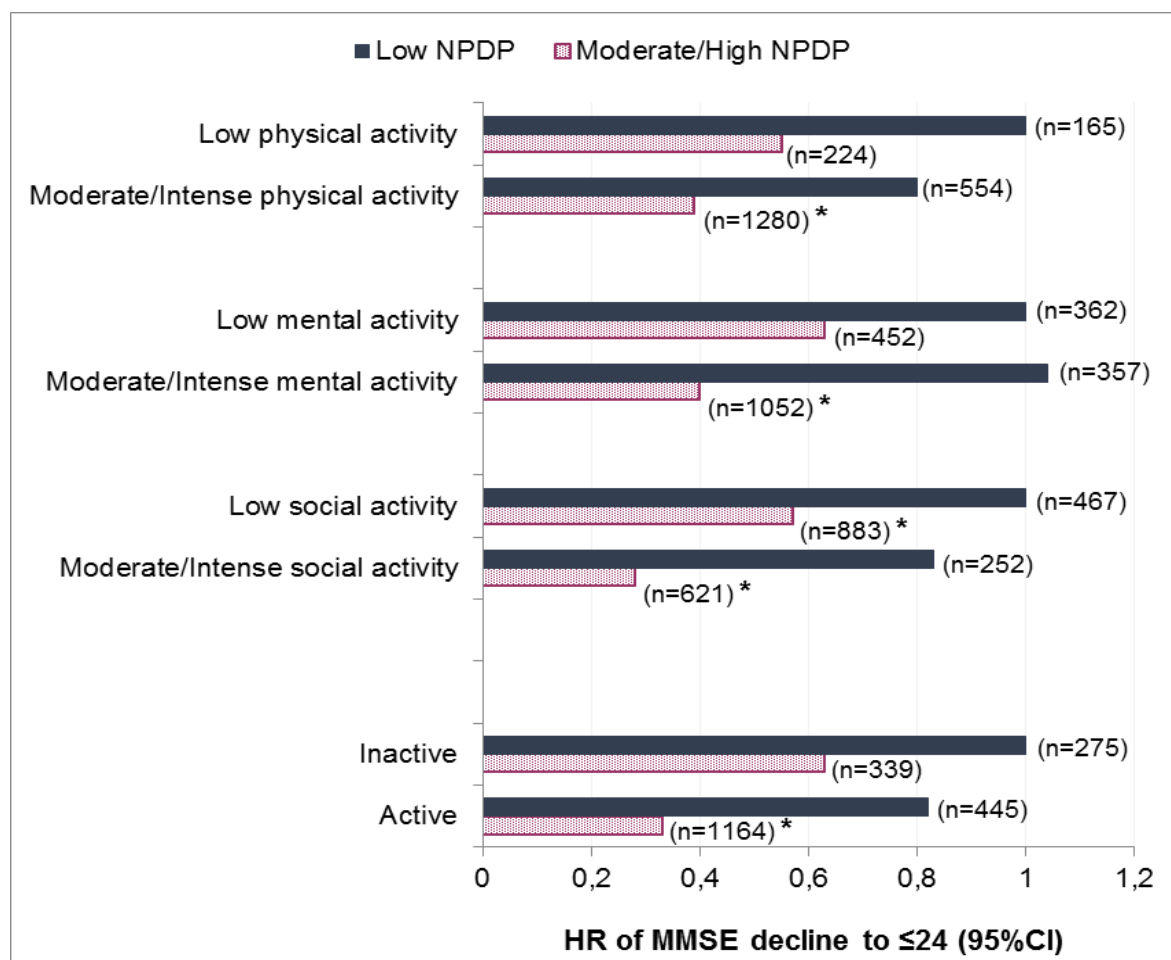


Figure 9. Hazard ratios (HR) of MMSE decline to ≤ 24 in relation to joint effect of the NPDP and leisure activities (adjusted for age, sex, education, civil status, total energy intake, dietary vitamin/mineral supplement use, smoking, body mass index, vascular disorders, cancer, diabetes, depression, *APOE* $\epsilon 4$, and other lifestyle factors). Low adherence to the NPDP and a low activity level/inactive lifestyle was the reference category in each model. **P*-value < 0.05 .

Leisure activity score was assessed as “0” if at least two of the three activity dimensions (physical, mental, social) were low, and the third one was low/moderate; “1” if two of the dimensions were moderate, and the third one was moderate/intense; and “2” if at least two of the dimensions were intense. An active lifestyle was defined as a leisure activity score of ≥ 1 (vs. 0 as inactive).

5.6 SENSITIVITY ANALYSES

In Study *I*, to control for the effects of the potential preexisting morbidities on survival, those who died during the first 3 years of follow-up were excluded from the analyses. Despite the slight attenuation in results, the associations between nutritional status and mortality remained statistically significant. Further adjustment for morbidities other than those included in the MNA-SF questionnaire, and also exclusion of participants that were living in institutions (n=62) did not change the findings. However, with the latter exclusion, a slight attenuation was observed in the prevalence of the poor nutritional status and in the standardized mortality rate in MNA-SF categories. Finally, when the analyses were repeated after imputation of missing data on MNA-SF items, the results were similar to those reported.

In Studies *II* to *IV*, there were no significant interactions between non-dietary covariates and time in any of the mixed-effects models. The associations between dietary patterns/indices or overall lifestyle and cognitive decline were not altered after introducing the interaction terms. In these studies, the effect of energy misreporting and undereating on the observed associations was examined by excluding those with under- or over-estimation of their total energy intake or possible undereating following standard criteria. In Study *III*, after this exclusion, the association between the continuous score of the BSD and cognitive decline was no longer significant. Finally, possible influence of imputation on the observed associations was examined by repeating the analyses in Studies *II* to *IV* with only those with complete SFFQ data (n=815). The results of these analyses were mostly similar to those from the initial analyses, except for the association between the MedDietScore and cognitive decline that was no longer significant in the high adherers in Study *III*.

6 DISCUSSION

6.1 MAIN FINDINGS

6.1.1 Nutritional status and survival

Poor nutritional status is prevalent in older adults, especially in nursing homes and hospital settings, and is commonly underestimated in general populations of older age. In Study *I*, MNA-SF data showed that 24.7% of Swedish older adults living in the community were at risk for malnutrition and that 1.7% were malnourished. So far, very few studies have used the MNA-SF to screen for poor nutritional status in community populations. A study of 2872 Taiwanese older individuals showed that 19% of the population was at risk for malnutrition and 3.5% had malnutrition.²⁸ However, in a European study on 309 German older community-dwellers who were receiving home care, about 41% were at risk for malnutrition, and about 15% were malnourished.²⁷ In agreement with these two studies, we found that being at risk for malnutrition and malnourished were associated with a 1.5- to 3-fold greater risk for death. The extent of the effect of poor nutritional status on survival (i.e. median age at death) was not reported in previous studies. We found that the median age at death in those at risk for malnutrition was 1.5 years younger than those with normal nutritional status, and that those who were malnourished died a median of 3 years younger than those with normal nutritional status.

Previous studies of traditional nutritional and inflammatory biomarkers have already shown that independently or in combination, low levels of haemoglobin, albumin and/or high levels of C-reactive protein are associated with poor nutritional status, mainly in elderly patients.¹⁴³⁻¹⁴⁶ The high prevalence of nutritional deficits and suboptimal levels of biochemical markers, the concomitant occurrence of these conditions in old age, and the multifactorial nature of all these variables makes it difficult to define the directionality of the associations. As an example, some studies suggest that malnutrition is an etiological factor in biomarkers suboptimal measures,¹⁴⁷ and others suggest that biomarkers suboptimal levels (e.g. low haemoglobin or anemia) are etiological factors that can be used in the diagnosis and management of malnutrition.⁹ To the best of our knowledge, there is no epidemiological evidence on how the combination of MNA-SF-defined nutritional status and traditional nutritional biomarker measures is related to survival in the general population of community-dwelling older adults. In Study *I*, we showed that poor nutritional status together with anemia and/or hypoalbuminemia was associated with shorter survival than poor nutritional status alone.

6.1.2 Dietary patterns and cognitive decline

During the last decade, several longitudinal studies have examined the association between overall dietary intake and cognitive function, mainly in older adults (**Table 3**).

In most of the dietary patterns examined in those studies, total vegetable and total fruit intake was considered in constructing most indices/factors. Exceptions include the Recommended Food Score (RFS) and the French alternative Mediterranean diet (MeDi) (potatoes were completely excluded), MIND (green leafy vegetables were separated from other vegetables, and berries were the only fruits included), and in the traditional Greek Mediterranean index (fruits were grouped together with nuts). Potatoes were included in some dietary patterns as a healthy item (MedDietScore), whereas in others they were considered a less healthy item (Western dietary pattern). Legumes/beans were included in all healthy patterns except RFS and the modified Alternative Healthy Eating Index (mAHEI). Fish was included in all healthy patterns. Although poultry was not taken into account in most MeDi indices that had scores of 0 to 9, in RFS, or in mAHEI, it was included in MIND as a healthy item, and in DASH and MedDietScore that had a score of 0 to 55 as a less healthy item. Red meat was included as a less healthy item in all patterns but the RFS, which considered lean meat healthy. Regarding the cereals and grains group, the 0- to 9-point MeDi included the total intake of cereals; the 0- to 55-point MedDietScore, MIND, mAHEI, and RFS included whole grains; the Western pattern included white bread; and DASH and HEI-2005 took the total intake of grains into account. Total dairy intake was considered a less healthy option in the 0- to 9-point MeDi. It was included in DASH as a healthy choice, whereas in the 0- to 55-point MedDietScore and the Western diet, full-fat dairy items were considered less healthy items. In HEI-2005 only milk, and in MIND, only cheese was considered. Alcohol intake was not taken into account in RFS and the prudent/Western patterns. Regarding fat intake, the MUFA/SFA ratio was included in the 0- to 9-point MeDi; deep-fried foods were considered in mAHEI; fast foods, olive oil, nuts, and butter/margarine were included in MIND; nuts, %E from total fat and from saturated fat were taken into account in DASH; and only olive oil as the major source of fat was considered in the 0- to 55-point MedDietScore.

In Study II, we detected two dominant eating patterns in Swedish older population; namely, the prudent and Western patterns. These patterns had many features similar to dietary patterns already defined in the literature; the prudent pattern emphasized more frequent intake of fruits and vegetables, cereals and legumes, whole grains, rice/pasta, fish, poultry, low-fat dairy products, and water. The Western pattern included more frequent intake of refined grains, potatoes, red/processed meats, eggs, high-fat spreads and dairy products, butter/margarine, sweets and sugar, fruit juice, (salty) snacks, soft drinks, beer, and spirits.

In line with the few available studies, we found less cognitive decline in those with higher adherence to the prudent pattern and more cognitive decline in those with higher adherence to the Western dietary pattern. The effects of concomitant adherence to both dietary patterns on cognitive function depended on the level of adherence to each pattern. Overall, higher adherence to the prudent diet resulted in attenuation of adverse effects of the Western diet on cognitive function.

One major concern when comparing different dietary patterns and indices is food groupings and classifications. Unfortunately, most studies do not present the exact list of foods included in each food group. To better understand the relationship between eating patterns and specific outcomes, it is necessary to know whether, for instance, the cumulative effect of intake of the entire fruits and vegetables family (regardless of its exact constituents) determines its health benefits or whether only specific combinations of fruits and vegetables exert such beneficial effects. With this in mind, researchers developed the MIND dietary index, which includes more specific food items with the potential to protect against cognitive impairment and dementia.¹⁰⁴ The results of the initial study of the effect of adhering to the diet represented by the MIND index were positive.¹⁰⁴ However, the study was conducted in an American population, and the effect needs to be explored in other populations. In our Swedish older population, higher adherence to the MIND was associated with less cognitive decline.

Discrepancies in the findings of studies on the same dietary patterns (e.g. Mediterranean diet) in different populations might be purely due to methodological heterogeneity or rooted in different population-specific underlying factors, such as lifestyle, food traditions, or culture that affect adherence levels to different diets. Dietary patterns are not static but are prone to ongoing change.¹⁴⁸ For this reason, researchers have suggested that even though the very traditional symbols of Mediterranean diet are wheat bread and olive oil, because of emerging hindrances such as gluten sensitivity, a “modernized” Mediterranean diet concept that is independent from geography, climate and culture would provide the opportunity to follow this eating pattern without olive oil or wheat bread consumption.¹⁴⁸ However, the extent of change/modification that is acceptable while still recognizing a dietary pattern as the Mediterranean diet remains to be elucidated. In fact, although the Mediterranean diet is a dietary pattern that has been the most extensively studied in relation to various health outcomes, it is not clearly defined. The Mediterranean region is geographically large and there are important differences in dietary composition in the countries in the region. For example, the Italian variant of the Mediterranean diet puts great emphasis on pasta consumption. In Spain, fish intake is particularly high, and in Greece, whole grain bread, cooked food, and salads rich in olive oil, vegetables and legumes are consumed in larger amounts.¹⁴⁹

Moreover, lack of detailed information on the type and amount of some individual food items or categories of food in different studies has obliged researchers to modify their dietary assessments and index constructs. Such deviations from the original proposed diet criteria may distort inferences about specific diet-cognition associations. In Study *III*, data were not available on intake of nuts and olive oil, which were thus replaced by vegetable oil intake in constructing the MedDietScore and MIND. In fact, the consumption of olive oil (MUFA) is generally low in Northern European populations, and vegetable oil intake mainly consists of intake of rapeseed oil, which contains about 30% PUFAs and 60% MUFAs.^{150, 151} Such modification might therefore be considered a region-specific adaptation of these dietary

indices. Previous researchers have suggested that construction of population-specific dietary indices would be an appropriate approach to studying diet-disease associations.^{152, 153}

In Study *III*, we developed a new dietary index (i.e. NPDP), which was made up of dietary items that had low inter-correlation and were independently associated with cognitive decline. The NPDP is similar to other healthy dietary indices in that it emphasizes more frequent intake of poultry and fish, moderate intake of wine, and less frequent intake of high-fat dairy products, butter/margarine, vegetable oil, and sweets. However, it is unique in that it encourages higher intake of non-root vegetables, apples/pears/peaches, pasta/rice, tea, and water and discourages high intake of root vegetables, refined grains/cereals, and fruit juice. The NPDP was associated with a lower rate of change in MMSE scores and a lower risk of a decline to MMSE scores of ≤ 24 over 6 years than other healthy dietary indices.

In summary, MIND is outcome-specific but not region-specific; the BSD is region-specific but not outcome-specific; and the MedDietScore and DASH are neither region-specific nor outcome-specific. The NPDP is both region-specific and outcome-specific. That could be the main reason behind the differences between the observed associations between the dietary indices and MMSE change and risk of clinically meaningful cognitive decline.

6.1.3 Joint effect of diet and an active lifestyle on cognitive decline

Physical inactivity is one of the most prevalent risk factors for cognitive decline and dementia in Europe.¹⁵⁴ The majority of studies on the relationship between physical activity and cognition have found a lower risk of cognitive decline in people who engaged in regular physical activity in midlife and/or late life.⁶⁷ In a recent meta-analysis, higher levels of physical activity were associated with a 35% lower risk of cognitive decline than lower levels of activity.¹⁵⁵ However, data on the prevalence of other types of leisure activities, including mental and social activities, and their association with cognitive function are scarce.^{66, 67} A few available studies on cognitively stimulating activities have shown an association between life-long (especially late-life) mental activities and lower rates of cognitive decline or risk of dementia.^{70, 156} In one study, past and current cognitive activities together accounted for 14% of the variability in cognitive changes over several years prior to death.¹⁵⁶ One study has shown that social network reduces the effects of Alzheimer's disease pathology (amyloid and tangles) on cognition in the late years of life.¹⁵⁷ In another study on the same cohort, perceived social isolation (loneliness) was associated with more rapid cognitive decline.¹⁵⁸

In Study *IV*, we found that the most common activities in the SNAC-K population were physical pursuits (>80% reported regular moderate to intense physical activities), followed by mental activities (63%), and social engagement (39%). In this study, each of the lifestyle factors was independently associated with less cognitive decline, including healthy diet (moderate to high adherence to NPDP) and the three dimensions of leisure activity (moderate

to intense physical, mental, or social activities). The combination of all these lifestyle factors was associated with even less cognitive decline.

The joint effect of lifestyle factors, as composites of diet and leisure activities, on cognitive function have recently been drawing attentions. However, to the best of our knowledge, no studies have so far examined the effect of composite of diet and all three activity dimensions on cognitive decline. In one North American study, simultaneous adherence to a Mediterranean-type diet and physical activity was associated with a 35% lower risk of Alzheimer's disease than low adherence to a Mediterranean diet and low physical activity levels.⁷⁵ In another North American study, six lifestyle factors, including adherence to the DASH diet, exercise, church attendance, social interactions, alcohol intake, and smoking, were used to group people into four distinct lifestyle classes: unhealthy-religious; unhealthy-non-religious; healthy-moderately religious; and healthy-very religious. Those in the second, third, and fourth classes showed 46%, 44%, and 42% lower risk for dementia and AD, respectively than those in the first class.⁶⁹

In Study IV, we showed that moderate to high adherence to a healthy diet (i.e. the NPDP), together with moderate to intense physical, mental, or social activity were related to a lower rate of change in MMSE scores and to 61%, 60%, and 72% lower risk of a decline to an MMSE score of ≤ 24 over 6 years, respectively. Moderate to high adherence to the NPDP was related to 37% lower risk of a decline in MMSE scores in those with low leisure activity levels. However, the addition of an active lifestyle (all three dimensions of activities together) could reinforce the protective effect of the NPDP, reducing the risk of decline to an MMSE score of ≤ 24 still further (67% lower risk).

6.1.4 Biological plausibility

Nutritional status and survival. Poor nutritional status is usually accompanied by different degrees of weight loss, which can lead to loss of fat, muscle mass, and even bone mass. As a consequence, older adults with compromised nutrition are more prone to falls and fractures. Nutritional deficiencies can lead to multiple problems, including weakness, fatigue, anemia, cognitive dysfunction, and immune dysfunction/infections. All these factors, if not treated, can decrease functionality and quality of life and increase morbidities, the number of hospital admissions and length of hospital stays, and consequently the risk of death.^{159, 160}

Diet, active lifestyle, and cognitive decline. Multiple causal mechanisms have been suggested as potential pathways underlying the associations between diet, leisure activities and cognitive decline. Most of these pathways are interlinked and result in similar pathophysiological responses. The possible mechanisms involved in the relationship between diet and leisure activities and cognitive dysfunction/cognition protection are summarized below.

1. Vascular pathway. One of the major pathophysiological processes in many vascular disorders is the activation of endothelium by an inflammatory stimulus and consequent development of atherosclerosis.^{161, 162} Several studies have shown an association between systemic atherosclerosis and cognitive impairment.¹⁶³ High consumption of saturated fat is a potential risk factor for vascular disorders, and high intake of antioxidant-rich foods such as fruits and vegetables, tea, and wine is associated with vascular health, including better endothelial function.¹⁶⁴ With regard to overall eating patterns, an improvement in endothelial function and a reduction in vascular inflammation have been found in those who adhered to a Mediterranean-style diet.¹⁶⁵

2. Oxidative stress. The high concentration of lipid in the brain and high use of oxygen in the metabolic activities of this organ make the brain highly prone to oxidative damage.¹⁶⁶ An imbalance between production of reactive oxygen species (ROS) and biological antioxidant defense can lead to apoptotic cell death of neurons and increased oxidative damage to DNA.¹⁶⁷ These damages can accelerate cognitive decline in old age. Antioxidant-rich foods, such as fruit and vegetables, nuts, red wine, legumes and whole grains, block oxidative-induced damages to brain cells and thus have neuroprotective potential.¹⁶⁷ Vitamins C, A, and E; omega-3 PUFAs (both plant-derived α -linolenic acid [ALA] and marine-derived long-chain eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]); MUFAs (mainly oleic acid in olive oil); and flavonoids are potent dietary antioxidants that can inhibit oxidative stress and neuroinflammation and therefore protective against cognitive aging.¹⁶⁷⁻¹⁷¹ In contrast, low dietary intake of vitamins B6 (dark leafy greens, beans, poultry, fish), B9 (fruits and vegetables, whole grains, beans), and B12 (red meat, poultry, fish, eggs, dairy products) may result in elevated homocysteine levels and consequently in oxidative stress and inflammation that may lead to accelerated cognitive decline.¹⁷²

3. Neuroinflammation. Inflammation, especially low-grade chronic inflammation, is common in old age. Systemic inflammation can lead to neuroinflammation in the brain, neuronal damage, and consequently, cognitive dysfunction.¹⁷³ The prevalence of preclinical disorders in old age makes it difficult to infer a causal link between lifestyle factors (e.g. diet) and neuroinflammation. However, several studies have found an association between specific dietary components, such as saturated fat and toxic trans-fatty acids, and increased peripheral pro-inflammatory markers such as CRP and the cytokines interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α).^{148, 173-175} These findings suggest that lifestyle factors play a potential role in inflammation-induced cognitive dysfunction. In turn, higher adherence to healthy plant-based diets has been linked to lower levels of CRP.¹⁷⁶ Extra virgin olive oil and wine are associated with less production of peripheral pro-inflammatory IL-6.¹⁷⁶ It is worth mentioning that the same nutrients from different dietary sources may induce different inflammatory reactions. For instance, saturated fat from butter have shown a more pronounced pro-inflammatory response in the hypothalamus than saturated fat from coconut oil.¹⁷⁷ In addition, sources of MUFA in Northern Europe and the United States include

mainly beef and pork,¹⁴⁸ whereas the major source of MUFA in Mediterranean countries is olive oil. This may explain the observed differences in physiological reactions (inflammatory responses) to MUFA intake in studies of MUFA and cognitive function.

4. Insulin resistance. Insulin is necessary for brain function because of its role in modulating glucose uptake and protecting the function, growth and survival of brain cells.¹⁶⁷ Under normal conditions, the plasma level of glucose in the brain is relatively stable.¹⁶⁷ Alteration in glucose levels can lead to metabolic disturbance, and consequent insufficient response to insulin concentrations can cause hyperglycemia and insulin resistance.¹⁷⁸ Chronic exposure to high glucose levels results in selective neuronal death, oxidative stress, chronic inflammation, endothelial dysfunction, and increased susceptibility of the blood-brain barrier to cerebral micro-vessel damage; factors that together may lead to cognitive dysfunction.^{179, 180} Low dietary intake of omega-3 fatty acids may predispose the brain to disturbances in insulin signaling and thus to cognitive dysfunction.¹⁸¹ In contrast, high dietary intake of foods with low glycemic index (e.g. rye bread) is beneficial to insulin sensitivity and cognitive function.¹⁸² With regard to overall dietary intakes, higher adherence to the prudent diet has been associated with better insulin sensitivity; and the Western dietary pattern has been associated with a higher risk of insulin resistance.¹⁸³

5. Molecular mechanisms. Synaptic plasticity, adult neurogenesis and neuronal function are potential mechanisms through which specific dietary components and other lifestyle factors can exert beneficial or detrimental effects on cognitive function.¹⁸⁴ A healthy diet, rich in omega-3 fatty acids, flavonoids, and antioxidants, together with physical activity, can improve neuronal function by increasing hippocampal brain-derived neurotrophic factor (BDNF) levels and reducing oxidative stress.^{181, 185} These lifestyle factors play an important role in maintaining synaptic structure, axonal elongation, and neurogenesis in the adult brain.¹⁸⁵

6. Cognitive reserve. The hypothetical capacity of the brain to tolerate more aging and pathological effects is referred to as the “brain reserve”. How flexibly and efficiently a person can make use of the available brain reserve depends on his or her “cognitive reserve”; that is, inter-individual differences in the ability to efficiently use the brain networks.¹⁸⁶ Cognitive reserve is a hypothetical concept and cannot be measured directly; however, epidemiological evidence suggests several factors as proxies for cognitive reserve, including education; engagement in physical, cognitive, and social activities; social network; and even dietary habits.^{186, 187}

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Study design

All studies included in this thesis were observational studies and had a prospective cohort design. In Study *I*, nutritional status was assessed at baseline, and deaths were detected during

follow-up; thus, the temporality is clear. In Studies *II* to *IV*, dietary data were collected before the occurrence of meaningful/influential cognitive decline. Thus, cognitive impairment was less likely to affect the dietary intake assessment (recall). Although preclinical cognitive deficits could remain undetected, with a prospective cohort study design and exclusion criteria applied at baseline, potential causal relationship between diet and cognitive function could be examined.

6.2.2 Sources of error

In epidemiological studies, there are two broad classes of error in estimations; random errors and systematic errors (or biases).⁵² These errors could happen at within- and between-individual levels and can be differential or non-differential.¹⁸⁸ Studies should be designed and analytical methods should be selected in a way to reduce as much random and systematic errors as possible to increase the precision and validity, and in total, accuracy of the estimates. The possible sources of different random errors and biases in this project are discussed in the section that follows.

a) Random error (random variation or lack of precision)

Random errors may generally occur through population sampling and measurements.⁵² Random error caused by population sampling can be reduced by selecting a larger sample. With regard to dietary (main exposure) data, random variation due to different day-to-day and episodic (e.g. seasonal) food intake and errors in measuring/estimating dietary consumptions on any one day could lead to random within-individual error.¹⁸⁸ Random between-individual error could also be present if only one measurement of food intake is used.¹⁸⁸ In this project, only one-time SFFQ measures, taken at baseline, were used. It was assumed that in the presence of the random between-individual error, underestimation of intake in some people was counterbalanced by overestimation of intake in other people. Thus, the reported mean of food intake in this large cohort would be close to the true mean of the population.¹⁸⁸ Such random error can be reduced by the use of repeated measures.

b) Systematic error (bias or lack of internal validity)

Systematic error can occur in all phases of observational studies, from study design to data collection, analysis, and interpretation of findings. The main types of systematic error in observational studies are selection bias, information bias, and confounding. The internal validity of the studies can be determined on the basis of the extent to which these systematic errors are reduced.

In this project, biases might have been present not in recruiting participants but in selecting and retaining them and in the assessment of nutritional status, measurement of dietary intake, measurement of other covariates, or assessment of cognitive function.¹⁸⁹ The possible sources of systematic errors in this thesis are discussed in more details below.

Selection bias

Selection bias mainly occurs during study design; for instance, when the recruited or the retained study sample is not truly representative of the population from which the sample was drawn. The common consequence of such bias would be differing estimates of the association between exposure and outcome in participants and non-participants or in those selected for analysis and those who were eligible but not included in the analysis.¹⁹⁰ In general, prospective cohort studies are less prone to selection bias than retrospective studies because at the time of selection, only exposure has occurred.⁵⁶ Non-response, the healthy-entrant effect, and attrition biases can contribute to selection bias.¹⁸⁹

Non-response bias. This type of bias may occur if non-response is associated with differential exposure and thus with outcome status. There is usually little information about the initial non-participants (i.e. non-respondents) in a prospective cohort study. In this project, the 1227 (813 women and 414 men) who were alive and eligible to participate but who declined to participate in the SNAC-K baseline examinations were in general older (29% of the 80+-year-olds vs. 24% of the 60-year-olds), and those aged 60 to 87 survived a shorter time after the beginning of SNAC-K than participants.¹⁹¹ However, in prospective cohort studies differential loss to follow-up (i.e. attrition) is a more important source of bias that will be discussed later.

Healthy-entrant effect. The people included in the studies in this doctoral project might have been nutritionally and cognitively healthier than the general population. Thus, the healthy-entrant effect might have been present in our studies because of lower rates of nutrition- and cognition-relevant morbidity and mortality in the included samples, especially in the early phases of the project. Such a comparison was not possible at the recruitment stage because of lack of relevant information from non-participants.

We initially excluded those with missing data on MNA-SF items in Study *I*. participants with missing data were, on average, more often women (77.3% vs. 63.6), older (84.3 years vs. 73.7 years) than those included in the study. They had lower levels of education (university, 16.1% vs. 31.3%) and more frequently had dementia (53.7% vs. 4.7%), anemia (18.9% vs. 9.4%), or hypoalbuminemia (18.6% vs. 6.9%). More of them lived alone (84.6% vs. 55.7%) or in institutions (40.1% vs. 2.0%). However, no significant differences were observed with regard to diabetes, cancer, depression, any vascular disorders, or high CRP. Moreover, in Studies *II* to *IV*, the 508 non-demented participants with >20% missing values in SFFQ who were excluded from the studies had different demographic and health characteristics than those included in the studies (**Table 5**), although the median baseline MMSE scores were not different. As old age, lower education, and chronic conditions are associated with mortality¹⁹² and cognitive decline,¹⁹³ the associations in this thesis might have been underestimated.

Attrition bias. Differential loss to follow-up in cohort studies may cause attrition bias. In our project, 141 participants in the older cohorts and 107 participants in the younger cohort died and 284 declined/moved during the study period. No significant differences between older participants and dropouts were found in the first follow-up with regard to demographics, baseline MMSE score, BMI, chronic conditions, or *APOE* $\epsilon 4$ status. However, dropouts were older (median age 82 vs. 79; $P < 0.001$) and less often *APOE* $\epsilon 4$ carriers (18% vs. 30%; $P = 0.015$) than participants in the second follow-up. In the younger cohort, dropouts were more often men (49% vs. 41%; $P = 0.017$) and more often had lower levels of education (university, 39% vs. 46%; $P = 0.009$) than participants. They had lower baseline MMSE scores (29 vs. 30; $P < 0.001$) and a higher proportion had vascular disorders (89% vs. 84%; $P = 0.032$), diabetes (36% vs. 27%; $P = 0.001$), and cancer (10% vs. 5%; $P = 0.003$). However, there were no significant differences in their age, marital status, the proportion who lived in an institution, BMI, depression, or *APOE* $\epsilon 4$ status.

Overall, attrition bias is more likely in younger cohorts. However, the high attendance rates in the older cohorts (~88% in the first and 91% in the second follow-up) and in the younger cohorts (~88% in the second follow-up) may reduce the selection bias due to attrition to a large extent.

Misclassification/Information bias

Information bias is a systematic error due to inaccurate measurements of the exposures and/or the outcomes. Inaccurate measurement of continuous variables causes a bias called measurement error, and inaccurate measurement of categorical variables causes a bias called misclassification or classification error.⁵² In general, measurement errors in univariate exposure models may lead to attenuation of regression coefficients or hazard ratios toward the null.¹⁹⁴ Such errors in multivariate exposure settings may bias the estimates in any direction.¹⁹⁴

Misclassification of exposures. In prospective cohort studies, since the exposure is assessed before the outcome happens, exposure measurement errors are assumed to be non-differential with respect to the outcome.⁵²

In Study *I*, it is possible that we misclassified some participants on the basis of MNA-SF scores because of possible measurement errors in self-reported items (e.g. food intake decline or recent weight loss). Regarding the biomarker measures, misclassification of severity of inflammatory status on the basis of CRP values was possible because the classification was population-specific and no standard unified cutoff for such classification exists.

In Studies *II* to *IV*, person-specific bias (i.e. the bias specific to each individual that can differ among individuals) might have been present in measuring dietary intakes with the SFFQ. This error might exist if the food item(s) important to a study participant (but not necessarily to all) was/were missing from the food frequency questionnaire or if the person

misinterpreted the question(s) about the food item(s).¹⁸⁸ If such systematic error occurred, even repeated measurements of food intake would not help reduce the error and estimate the individual's true mean intake because the same error would occur in all measurements. The more careful design of the questionnaire, use of a combination of dietary assessment methods, and energy-adjustment of food/nutrients intake could be ways to reduce the effect of such errors on estimations.¹⁸⁸ Systematic between-individual errors result from systematic within-individual errors that affect study participants non-randomly. For instance, missing a commonly consumed food item in the food frequency questionnaire or using an incorrect nutrient composition value for a common food will affect all participants in the same direction but not to the same degree, because people may consume different amounts of those foods.¹⁸⁸ Since it is uncommon for systematic within-individual errors to have an equal effect on all people, systematic between-individual errors are usually inevitable.¹⁸⁸

Misclassification of participants' dietary adherence and activity levels in Studies *III* and *IV* cannot be ruled out because data were self-reported, and there are no standardized and homogenous cutoffs for calculating dietary index scores, calculating levels of adherence to dietary patterns, and estimating levels of activity. Moreover, the use of population-specific median food intakes to score people's dietary adherence levels can lead to misclassification of dietary exposure.¹⁹⁵ However, since the aim of our study was to propose a population-specific eating pattern with cognitive protective potential, such misclassification is negligible in this study. However, it needs to be taken into account in the future external validity assessments of the proposed eating pattern.

Partial non-response among participants may result in missing data on some variables that could affect exposure or outcome data and thus bias association estimates.¹⁹⁶ To assess the possible bias in estimations due to missing data, we applied the multiple imputation and compared estimates from complete-case analysis and imputed data analysis in each study.

Misclassification of outcomes. The outcome in Study *I* was not prone to misclassification because of timely and accurate records of all deaths in the Swedish Cause of Death Register.¹²⁰ Regarding the outcome assessment in Studies *II* to *IV*, one might argue that the MMSE is not a sensitive tool for detecting cognitive changes and that using the MMSE alone could have resulted in misclassification of baseline and follow-up cognitive functioning. In these studies, prevalent dementia cases at baseline were excluded via a valid diagnostic procedure.¹²¹ To reduce the probability of including participants with concealed emerging cognitive deficits, those people without dementia but with MMSE score of <27 were also excluded. The MMSE is a reliable screening tool for monitoring the rate of change in global cognitive function when scores over time are compared to baseline MMSE scores,¹⁹⁷ and change in global cognitive function was the main outcome in the studies included in this thesis. Moreover, the MMSE is sensitive enough to detect dietary-induced cognitive changes in cognitively intact people.¹⁹⁸ Still, it is worth acknowledging the possible ceiling effect or

lower sensitivity of MMSE for detecting mild cognitive impairment in the highly educated SNAC-K population.¹⁹⁹

Confounding

A confounder is a factor that is independently associated with both the exposure and outcome. Confounding, if not taken into account, can distort the observed effect estimates toward either overestimation or underestimation, depending on the direction of the observed associations.⁵² It can even change the direction of the observed associations.⁵² Despite a multitude of exposures and potential confounders that were taken into account in this thesis, as in all observational studies, residual confounding could still be a concern because it is impossible to adjust for unknown or unmeasured confounders.²⁰⁰

In Study *I*, to partially control for the confounding effect of any potential preexisting occult morbidity on the association between nutritional status and mortality, those who died during the first three years after baseline examination and those who lived in an institution were excluded in the sensitivity analyses. Such confounding could affect the estimates of mortality associated with poor nutritional status, creating a bias toward greater risk.²⁰¹ However, the estimates of the association between nutritional status and survival remained stable in those sensitivity analyses.

One important confounder in studies of dietary intakes and any health outcome is total energy intake. Total energy intake might be a primary determinant of cognitive function, or if the energy intake is associated with cognitive decline risk but is not a direct cause of cognitive decline, it is likely that associations with specific food/nutrients are confounded by total energy intake.¹⁸⁸ Some part of variation in food consumption might also be due to variation in total energy content of the foods. To isolate the variation in food/nutrients intake and check the association between food/nutrients composition and cognitive function, food/nutrients should be energy-adjusted.¹⁸⁸ Thus, in studies with dietary exposures, energy-adjusted dietary variables should be used, and also the association estimates should be adjusted for total energy intake.¹⁸⁸ Some previous studies have not clearly stated whether they have taken either or both such confounding effects into account.^{90, 106, 108} Both procedures were applied in Studies *II* to *IV* in this thesis.

6.2.3 Generalizability (external validity)

In epidemiological studies, external validity refers to the applicability of the findings of a study to populations other than the study population. Traditionally, selection bias has been considered the major reason for the variation in the external validity of observational studies. However, it is very difficult, if not impossible, to select a study sample that is fully representative of all other populations, as any given population always has unique characteristics. For instance, the SNAC-K population is generally healthier and of higher socioeconomic status than the population of Stockholm as a whole or of Sweden.^{191, 202}

The principles of statistical inference assume that the findings of a study are applicable only in circumstances similar to those of the study itself and to people who resemble those in the study population.²⁰³ Accordingly, caution is needed in generalizing the results of the studies in the current thesis to other populations. However, the statistical inference should not be confused with scientific inference. A representative sample may enhance the statistical inference, and it can be useful in doing purely descriptive studies. Nonetheless, in most cases, it is not the representativeness of the study population that improves the generalizability of the findings, but the knowledge of specific conditions and understanding of mechanisms that enables proper generalization (e.g. findings about the protective effect of vegetable intake against cognitive decline would be applicable in most populations).²⁰³ When scientific inference is possible, scientific findings are more likely to be reproducible.²⁰³ Internally valid studies could help us to advance our understanding of causal mechanisms and enhance generalization. The findings of this thesis might be generalizable to other populations with similar confounding characteristics and studies with a similar level of internal validity.

7 CONCLUSIONS

1. Malnutrition and risk for malnutrition (poor nutritional status) were present in about a quarter of the community-dwelling older adults in our study population and were associated with shorter survival. Poor nutritional status combined with low haemoglobin and albumin levels may lead to an even younger age at death.
2. The dominant dietary patterns among Swedish people ≥ 60 years were the prudent and Western dietary patterns. The prudent dietary pattern was associated with less and the Western dietary pattern to more cognitive decline. High adherence to the prudent diet may diminish the adverse effects of high adherence to the Western diet on cognition.
3. The Nordic Prudent Dietary Pattern (NPDP) was identified as a dietary pattern index associated with a lower rate of cognitive decline in Swedish older adults. The NPDP predicted decline to an MMSE score of ≤ 24 better than other healthy dietary indices, including MIND, the MedDietScore, DASH, and the BSD. Moderate to high adherence to the NPDP may predict better preserved cognitive function in people in Nordic countries.
4. An active lifestyle more than doubled the protective effect of moderate to high adherence to the NPDP against cognitive decline and lowered the risk of declining to an MMSE score of ≤ 24 by an additional 30%.

8 RELEVANCE AND IMPLICATIONS

The number of older adults at risk for progressive cognitive decline and dementia is rapidly growing in the whole world. Thus, one of the current public health priorities is to maintain or improve cognitive functioning and related quality of life well into older age to delay the onset of dementing disorders. Researchers estimated that more than 20% of dementia cases expected globally by 2050 could be avoided entirely if the start of the disease was delayed by only 2 years in 2010.²⁰⁴ Therefore, keeping the long latency period for cognitive impairment and dementia in mind, the timely detection of people at risk and application of appropriate preventive strategies is highly relevant to reduce the individual and societal burden of cognitive dysfunction.

Risk factors modification is a crucial strategy for preserving cognitive health. The findings of the current population-based thesis highlight the importance of lifestyle factors, especially of diet, in accelerating or decelerating the process of cognitive deterioration. In addition, the findings provide better insight into the high risk of undetected malnutrition in older community-dwellers and into the extent to which poor nutritional status in old age, in combination with anemia and hypoalbuminemia, may contribute to shorter survival. Accordingly, from both public health and clinical perspectives, it would be relevant to regularly screen older adults' nutritional status so that we can intervene in a timely manner to help those who are at higher risk for losing life years due to compromised nutrition.

9 FUTURE DIRECTIONS

The heterogeneous findings of diet-cognition studies in the literature suggest that we need methodological improvements in assessing both dietary intakes and cognitive function. Moreover, slight differences in foods that had a significant effect on global cognitive changes in the studies in this thesis than in previously proposed diets suggest that such associations should perhaps be investigated at the country or even the regional level. However, to confirm or reject this suggestion, the external validity of the findings in this thesis must be tested not only in other Nordic countries, but also in non-Nordic older populations.

Furthermore, more comprehensive cognitive evaluations are needed to assess different cognitive domains in relation to the NPDP and an active lifestyle. Data from a number of multidomain interventions to prevent cognitive impairment and dementia are currently being analyzed and other such interventions are underway. Given the high inter-correlation between lifestyle factors, a single-domain approach (e.g. focusing on only dietary or only physical activity modifications) does not seem promising. However, data on this topic are scarce. A recent 2-year multidomain intervention to prevent cognitive decline in at-risk older adults from the general population, and which included diet, physical exercise, cognitive training, and vascular risk monitoring, was successful in maintaining or improving cognitive functioning in the intervention group.²⁰⁵ In that intervention study, dietary modifications were based on general national nutrition recommendations. Had the modifications been outcome-specific, the results might have been even better. Whether and to what extent the dietary and activity modifications proposed in this thesis can delay the progression of cognitive decline to cognitive impairment and dementia can be examined in form of a multidomain intervention.

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12 APPENDICES

12.1 APPENDIX 1. FOOD ITEMS INCLUDED IN THE SFFQ IN SNAC-K

Food groups			Food items
Vegetables, potatoes)	total	(incl.	Tomato; cucumber; carrot, other root veg (e.g. turnip, parsnip); white and red cabbage; lettuce, Chinese cabbage; spinach, kale or borecole; cauliflower, Brussels sprouts, broccoli; mushrooms; frozen vegetable mix; vegetable casseroles; vegetable gratin; cooked/baked potatoes; mashed potatoes; potato salad
Fruits, total			Berries (fresh or deep-frozen); apples, pears, peaches; orange, mandarin, grapefruit; banana
Grains/cereals, total			White bread; tick soft whole grain bread; hard bread, crisp hard-rye bread (e.g. Husmans); wheat crisp flat bread, light oven flat bread; crackers; porridge of oatmeal, rye or barley; porridge of semolina or grain of rice; Gruel; fiber-rich cereals (e.g. musli); corn flakes; rice; spaghetti, macaroni
Legumes/beans			Red beans, pea soup; other beans soup
Meat (red/processed), total			Minced meat (e.g. meatballs, hamburger, mincemeat sauce); meat casseroles; whole meat (e.g. roast meat, cutlet); liver, kidney; sausages cold cuts; meat toppings; Liver pâté; bacon, flitch of bacon; sausage dish; blood meal (e.g. blood sausage, blood pudding)
Poultry			Chicken or any other birds
Fish			Lean fish (e.g. bass, codfish, coalfish); fatty fish (e.g. herring, Baltic herring, whitefish, salmon, mackerel, eel); pickled fish (e.g. salt herring, Baltic herring); shellfish (e.g. shrimp, clam, crayfish); fish gratin
Eggs			Egg and egg dish
Dairy products, total			Low-fat hard cheese 10-17% ; soft cheese, whey cheese; low-fat milk 0.5%, 0.1%, low-fat sour milk; light yoghurt, Hälsofil; medium-fat hard cheese 28%; medium-fat milk, medium-fat soured milk 1.5%; cream, crème fraîche, sour cream; full-cream cheese, dessert cheese; standard-fat (normal) milk, soured milk 3%; yoghurt, kefir
Spreads, total			Bregott for sandwich (sort of butter); butter for sandwich; margarine for sandwich (e.g. Flora, Runda bords); low-fat margarine for sandwich (e.g. Lätt & Lagom, Lättlätt)
Cooking fat			Butter for cooking; Margarine for cooking (e.g. Milda, Eve, Ädel, TreEss)
Cooking/dressing oils			Vegetable oils for cooking; vegetable oils for salad dressing
Sweets/sugar/pastries			Sweet, goody (not chocolate); chocolate; marmalade, jam; lump of sugar, powdered sugar or castor sugar, honey; pancake, waffle; tart, cake pieces; confectionaries (e.g. Mazarin); coffee bread
Ice cream			Ice cream
Fast food			Fried potatoes, potato balls; French fries; burger; pizza
Snacks (salty)			Chips, popcorn, salt nuts
Non-alcoholic beverages			Carbonated drinks (e.g. Coca-cola, fanta, 7up, sprite, etc.); coffee (filter; boiled); tea; fruit juice (e.g. juice; fruit syrup, nectar; Rose-hip creamy juice, fruit soup creamy juice); water (plain, mineral)
Alcoholic beverages			Low-alcohol beer; medium-strong beer; double-strength bock beer; white wine; red wine; liquor

12.2 APPENDIX 2. DIETARY COMPONENTS OF EACH DIETARY INDEX AND DISTRIBUTION OF TOTAL SCORES FOR EACH INDEX IN SNAC-K

Dietary components	NPDP 15 items	MIND 14 items	MedDietScore 11 items	DASH 10 items	BSD 9 items
Vegetables	Non-root vegetables	Green leafy vegetables	Potatoes	Total vegetables	Vegetables other than potatoes plus legumes
	Root vegetables	Vegetables other than green leafy	Vegetables other than potatoes		
Fruits	Apples/pears/peaches	Berries	Total fruits	Total fruits	Apples/pears/peaches plus berries
Grains/cereals	Refined grains/cereals	Whole grains	Whole grains	Total grains/cereals	Oats/rye bread/porridge
	Pasta/rice				
Legumes/beans		Legumes/beans	Legumes/beans	Legumes/beans	
Red meat, poultry, fish		Red/processed meat	Red/processed meat	Total red meat, poultry, fish	Red/processed meat
	Poultry	Poultry	Poultry		
	Fish	Fish	Fish		Fatty fish
Dairy products	High-fat dairy products	Cheese	High-fat dairy products	Total dairy products	Milk <2% fat
Butter/margarine	Butter/margarine	Butter/margarine			
Vegetable oil	Vegetable oil	Vegetable oil	Vegetable oil		
Sugar/sweets/pastries	Sugar/sweets/pastries	Sugar/sweets/pastries		Sugar/sweets/pastries	
Fast/fried food		Fast/fried food			
Alcohol	Wine, drink F: >0 & ≤1 M: >0 & ≤2	Wine, drink F: >0 & ≤1 M: >0 & ≤2	Wine, drink F: >0 & ≤1 M: >0 & ≤2		Total alcohol, g F: >0 & ≤10g M: >0 & ≤20g
Tea	Tea				
Fruit juice	Fruit juice				

Water (plain/mineral)	Water (plain/mineral)				
Other items than food/beverages					
				Sodium	
				E% from fat	E% from fat
				E% from saturated fat	Fatty acid ratio PUFA:(SFA+Trans) [*]
Distribution of index scores					
Total possible score	0 to 71	0 to 66	0 to 51	0 to 50	0 to 41
Score range in SNAC-K	8 to 62	4 to 57	1 to 44	2 to 48	0 to 39
Men	10 to 59	4 to 57	1 to 44	2 to 48	1 to 39
Women	8 to 62	7 to 56	1 to 42	5 to 45	0 to 38
Median (IQR) score in SNAC-K	33 (27, 40)	30 (24, 36)	19 (15, 24)	25 (20, 30)	16 (12, 21)
Men	33 (27, 41)	29 (24, 36)	19 (14, 24)	25 (20, 30)	16 (12, 21)
Women	33 (27, 40)	30 (24, 36)	19 (15, 24)	25 (20, 30)	16 (12, 21)

12.3 APPENDIX 3. LIST OF DISSERTATIONS FROM THE AGING RESEARCH CENTER AND THE STOCKHOLM GERONTOLOGY RESEARCH CENTER, 1991-2016

1991

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

1992

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

1993

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

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

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

1994

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

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

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

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

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

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

1996

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

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

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

1997

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

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

1998

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

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

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

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

1999

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

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

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

2000

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

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

2001

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

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

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

2002

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

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

2003

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

2004

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

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

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

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

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

2005

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

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

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

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

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

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