From the Aging Research Center
Department of Neurobiology, Care Sciences and Society
Karolinska Institutet, Stockholm, Sweden

Cardiovascular Health, Orthostatic Hypotension, and Cognitive Aging

Xin Xia
夏昕

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Cardiovascular Health, Orthostatic Hypotension, and Cognitive Aging

Thesis for Doctoral Degree (Ph.D.)

By

Xin Xia (夏昕)

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Principal Supervisor:
Associate Professor Davide Liborio Vetrano
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging Research Center

Co-supervisors:
Associate Professor Chengxuan Qiu
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging Research Center

Associate Professor Debora Rizzuto
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging Research Center

Associate Professor Erika J Laukka
Karolinska Institutet
Department of Neurobiology,
Care Sciences and Society
Aging Research Center

Opponent:
Professor Roman Romero-Ortuno
Trinity College Dublin
School of Medicine

Examination Board:
Professor Yvonne Forsell
Karolinska Institutet
Department of Global Public Health

Associate Professor Karin Modig
Karolinska Institutet
Institute of Environmental Medicine

Professor Peter M Nilsson
Lund University
Department of Clinical Sciences

To my mom and dad.

致我的妈妈和爸爸。

“Den som är väldigt stark måste också vara väldigt snäll.”

“If you are very strong, you must also be very kind.”

“如果你很强大，你一定也很善良。”

Astrid Lindgren, Pippi Långstrump

Popular science summary of the thesis

Dementia in the aging world

The number of people living with dementia is rising as the proportion of older adults across the world increases. People with dementia have difficulties with thinking, such as memorizing things and planning activities, and gradually lose the ability to manage their lives independently. Dementia is a clinical syndrome that can result from several diseases that lead to the death of brain cells, such as Alzheimer's disease. Although aging is the strongest risk factor for dementia, dementia is not inevitable with age. Environmental factors, lifestyle factors, and many other factors can all influence the development of dementia. Cardiovascular health is one of the important factors that can impact dementia development, and people with better cardiovascular health are less likely to develop dementia.

What questions does the thesis want to answer?

There is a tool, Life's Simple 7, that sets the goal for people to achieve and maintain ideal cardiovascular health. Life's Simple 7 sets the ideal goals of seven factors: smoking, physical activity, body mass index, healthy diet, blood pressure, blood sugar, and total blood cholesterol. This thesis tried to understand if achieving the goals of Life's Simple 7 can protect against dementia and expand one's years of life with normal thinking abilities. The thesis also investigated whether orthostatic hypotension – a significant drop in blood pressure after standing up – might affect the development of cardiovascular diseases and dementia.

How did we answer these questions by conducting epidemiological studies?

Epidemiological studies investigate how often a disease occurs and which factors can affect the occurrence of the disease in populations. In this thesis, we conducted epidemiological studies using secondary data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), a study of more than 3000 people aged ≥60 years who lived in Kungsholmen, a central area of Stockholm, Sweden. The SNAC-K study started between 2001-2004. During these years, the cardiovascular health levels and orthostatic hypotension status of the study participants were evaluated. Then, the SNAC-K staff have regularly evaluated the health of the study participants every three or six years since the start of the study. We then compared the frequency of dementia occurrences in participants with different cardiovascular health levels and orthostatic hypotension status.

What did we find, and what do the findings mean?

We found that people aged under 78 years with better cardiovascular health were less likely to develop dementia, more likely to live longer, and had more life years with normal thinking abilities. We also found that people with orthostatic hypotension were more likely to develop cardiovascular diseases and dementia. These findings suggest that

maintaining good cardiovascular health and preventing orthostatic hypotension might reduce the risk of developing dementia.

老龄化世界中的痴呆症

随着世界各地老年人比例的增加，患有痴呆症的人数也在逐年增加。患有痴呆症的人会出现思维困难，例如无法正常记忆事物和计划活动，并逐渐失去独立管理生活的能力。痴呆症可由多种可导致脑细胞死亡的疾病引起，包括阿尔茨海默病。虽然衰老是痴呆症的最显著的危险因素，痴呆症并非衰老过程中无法避免的结局。环境、生活方式和其他因素都会影响痴呆症的发展。心血管健康是影响痴呆症发展的重要因素之一，心血管健康状况较好的人患痴呆症的风险也更小。

这本论文想要回答哪些研究问题？

有一个名为"简单生活 7"的工具，它为七个重要的影响心血管健康的因素设定了理想目标。这七个因素包括吸烟、体重指数、身体锻炼、健康饮食、血压、血糖和血液胆固醇水平。本论文试图研究实现"简单生活 7" 的目标是否可以预防痴呆症并延长无痴呆症的生命时间。该论文还试图研究一种可能影响心血管健康和痴呆症发展的新因素，即直立性低血压。直立性低血压是指站立后血压急剧下降的一种情况。

我们如何通过流行病学研究来回答这些问题？

流行病学研究研究疾病发生的频率以及哪些因素会影响该疾病在人群中的发生与发展。在本论文中，我们利用瑞典老龄化与护理研究(SNAC-K)的数据进行了流行病学研究，该研究对瑞典首都斯德哥尔摩市中心的三千多名 60 岁及以上的居民进行了研究。SNAC-K 研究于 2001 年至 2004 年间开始并一直进行到现在。SNAC-K 工作人员对研究参与者的心血管健康水平、直立性低血压状态、以及其他健康状况定期进行评估。然后，我们利用收集到的数据比较了不同心血管健康水平和直立性低血压状态下痴呆症的发生频率。

我们的研究发现了什么？这些研究结果的意义是什么？

我们发现，心血管健康状况更好的人患痴呆症的风险更低，并且没有思维能力障碍的寿命更长。我们还发现，有直立性低血压的人之后患心血管疾病与痴呆症的风险会更高。这些发现表明，维持理想的心血管健康和控制直立性低血压可能会有助于减小老年人患痴呆症的风险。

Demens i den åldrande världen

Antalet människor som lever med demens ökar med den ökande andelen äldre över hela världen. Människor som har demens har svårigheter med att tänka, memorera saker och planera aktiviteter, och förlorar gradvis förmågan att hantera sina liv självständigt. Demens kan orsakas av flera sjukdomar, inklusive Alzheimers sjukdom, som leder till att hjärnceller dör. Även om åldrande är den största riskfaktorn för demens är demens inte oundviklig vid åldrande. Miljö-, livsstilsfaktorer och många andra faktorer kan alla påverka utvecklingen av demens. Kardiovaskulär hälsa är en av de viktiga faktorerna som kan påverka utvecklingen av demens, och personer med bättre kardiovaskulär hälsa är mindre benägna att utveckla demens.

Vilka frågor vill avhandlingen besvara?

Det finns ett verktyg, Life's Simple 7, som sätter mål för människor att uppnå och upprätthålla en idealisk kardiovaskulär hälsa. Life's Simple 7 använder sig av sju kardiovaskulära faktorer för att sätta idealiska mål: rökning, body mass index, fysisk aktivitet, hälsosam kost, blodtryck, blodsocker och kolesterol i blodet. Den här avhandlingen försökte förstå om att uppnå målen i Life's Simple 7 kan skydda mot demens och utöka levnadsåren att leva med normala tankeförmågor. Avhandlingen undersökte också en ny faktor som kan påverka utvecklingen av hjärt-kärlsjukdomar och demens, ortostatisk hypotoni, som är ett drastiskt blodtrycksfall efter att man har ställt sig upp.

Hur svarade vi på dessa frågor genom att genomföra epidemiologiska studier?

Epidemiologiska studier studerar hur ofta en sjukdom uppstår och vilka faktorer som kan påverka uppkomsten av sjukdom i befolkningen. I denna avhandling har vi genomfört epidemiologiska studier med hjälp av sekundära data från Svenska Nationella Studien om Åldrande och Vård-Kungsholmen (SNAC-K), en studie av mer än 3000 personer i åldern ≥60 år som bodde på Kungsholmen, centrala Stockholm, Sverige. SNAC-K-studien startade mellan 2001-2004. Under dessa år utvärderades studiedeltagarnas kardiovaskulära hälsonivåer och ortostatisk hypotonistatus. Sedan utvärderade SNAC-K-personalen regelbundet hälsan hos studiedeltagarna vart tredje eller sjätte år. Vi jämförde sedan frekvensen av uppkomsten av demens över olika kardiovaskulära hälsonivåer och ortostatisk hypotonistatus.

Vad hittade vi och vad betyder fynden?

Vi fann att personer med bättre kardiovaskulär hälsa var mindre benägna att utveckla demens och mer benägna att leva längre utan svårigheter med tankeförmåga. Vi fann också att personer med ortostatisk hypotoni var mer benägna att utveckla hjärt-kärlsjukdomar och demens. Dessa fynd tyder på att bibehållande av god kardiovaskulär hälsa och hantering av ortostatisk hypotoni kan minska risken för att utveckla demens.

La demenza nel mondo che invecchia

Il numero di persone affette da demenza sta aumentando parallelamente all'aumento della percentuale di anziani in tutto il mondo. Le persone colpite da demenza hanno difficoltà cognitive, come la memorizzarione delle informazioni e la pianificazione delle attività, e progressivamente perdono la capacità di gestire in modo autonomo la propria vita. La demenza è una sindrome clinica che può derivare da varie malattie, come il morbo di Alzheimer, che provoca la morte delle cellule cerebrali. Sebbene l'invecchiamento sia il principalefattore di rischio per la demenza, questa non è inevitabile durante l'avanzamento dell'età. Fattori ambientali, uno stile di vita poco idoneo e molteplici altri fattori possono influire sullo sviluppo della demenza. La salute cardiovascolare si configura come uno dei fattori rilevanti che possono condizionare l'insorgere della demenza, dimostrando che le persone con una migliore salute cardiovascolare hanno menori probabilità di manifestare la demenza.

A quali domande vuole rispondere la tesi?

Esiste uno strumento, Life's Simple 7, che stabilisce gli obiettivi di mantenimento di una salute cardiovascolare ottimale. Life's Simple 7 identifica gli obiettivi ideali per i sette fattori chiave: il fumo, l'indice di massa corporea, l'attività fisica, una dieta sana, la pressione sanguigna, i livelli di glicemia e il colesterolo ematico. L'obbiettivo principale di questa tesi è di comprendere se il raggiungimento degli obiettivi definiti da Life's Simple 7 possa effettivamente contribuire alla prevenione della demenza e all's estenzione gli anni di vita vissuti mantenendo intatta la funzione cognitiva. Inoltre, la tesi si prefigge di investigare se l'ipotensione ortostatica – un drastico calo della pressione sanguigna dopo essersi alzati in piedi – possa influenzare lo sviluppo della demenza.

Come abbiamo risposto a queste domande conducendo studi epidemiologici?

In questa tesi, abbiamo condotto studi epidemiologici impiegando dati secondari provenienti dello Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), uno studio condatto su un campione di oltre 3000 persone di età ≥60 anni che vivevano a Kungsholmen, un'area centrale di Stoccolma, Svezia. Lo studio SNAC-K è stato avviatotra il 2001 e il 2004. Durante questi anni sono stati valutati i livelli di salute cardiovascolare e lo stato di ipotensione ortostatica dei partecipanti allo studio. Lo staff dello studio SNAC-K ha seguito regolarmente lo stato di salute dei partecipanti ad intervalli di tre o sei anni. Abbiamo quindi confrontato la frequenza di occorrenza della demenza tra diversi livelli di salute cardiovascolare e lo stato di ipotensione ortostatica.

Cosa abbiamo trovato e cosa significano i risultati?

Abbiamo rilevato che le persone con un migliore stato di salute cardiovascolare presentavano un minore rischio di sviluppare demenza e maggiori probabilità di vivere più a lungo senza difficoltà con le capacità di pensiero. Inoltre, abbiamo scoperto che le persone con ipotensione ortostatica avevano maggiori probabilità di sviluppare malattie cardiovascolari in assenza di problemi cognitivi. Questi risultati suggeriscono che il

mantenimento di una buona salute cardiovascolare e la prevenzione dell'ipotensione ortostatica potrebbero ridurre il rischio di einsorgenza della demenza.

Abstract

Cardiovascular health (CVH) plays an important role in dementia development. Ideal CVH, defined by Life's Simple 7 (LS7), has been associated with a lower risk of dementia in older adults. Orthostatic hypotension (OH) may be a novel cardiovascular risk factor that can affect dementia development. In this thesis, population-based cohort studies were conducted to investigate the role of LS7-defined CVH and OH in cognitive aging in people aged ≥60 years using data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K).

Study I investigated LS7-defined CVH in relation to transitions between normal cognition, cognitive impairment, no dementia (CIND), and dementia. The study found that people with better CVH had a lower hazard of transitioning directly from normal cognition to CIND (HR = 0.76, 95% CI = 0.61-0.95) and dementia (HR = 0.42, 95% CI = 0.21-0.82) in people aged <78 years. In addition, people aged <78 years with better CVH had two to three more years of life living with normal cognition. However, CVH, defined by LS7, was not related to transitions between cognitive states in people aged ≥78 years.

Study II evaluated the associations between OH and dementia. Of the 2532 people who were initially free of dementia, 615 (24.3%) people had OH. People with OH had higher hazards of developing dementia (HR = 1.40, 95% CI = 1.10–1.76) and Alzheimer's disease (HR = 1.39, 95% CI = 1.04–1.86). In addition, OH was related to a higher hazard of progression from CIND to dementia in people with CIND (HR = 1.54, 95% CI = 1.05–2.25) but not with incident CIND in those without CIND and dementia (HR = 1.15, 95% CI = 0.94–1.40).

Study III investigated the impact of OH on the development of CVDs and dementia in people initially free of CVDs as well as the impact of OH on dementia development in people with CVDs. The study found that in people who were initially free of CVDs, individuals who had OH at baseline had a higher hazard of developing CVDs (HR = 1.33, 95% CI = 1.12-1.59) but not dementia (HR = 1.22, 95% CI = 0.83-1.81) compared to those without OH. Among those with CVDs, persons with OH also had a higher hazard of dementia (HR = 1.54, 95% CI = 1.06-2.23) compared to those without OH.

Study IV assessed the associations of OH, in the presence or absence of frailty, with dementia and mortality. This study found that individuals who had OH at baseline had a higher hazard of dementia in the presence (HR = 2.73, 95% CI = 1.82-4.10) and absence (HR = 2.28, 95% CI = 1.47-3.54) of frailty than robust persons without OH. However, OH was only associated with a higher hazard of death without dementia when accompanied by frailty (HR = 1.56, 95% CI = 1.25-1.96).

Conclusions. Maintaining ideal CVH may protect against cognitive dysfunction and reduce years of life with cognitive dysfunction in younger old age. OH may be a potential modifiable risk factor for dementia, and the intermediate development of CVDs may help explain the association between OH and dementia.

Keywords. Cardiovascular health, Life's Simple 7, orthostatic hypotension, cognitive dysfunction, cohort study, older adults.

List of scientific papers

I. **Xia X**, Qiu C, Rizzuto D, Grande G, Laukka EJ, Fratiglioni L, Guo J, Vetrano DL. The age-dependent association of Life's Simple 7 with transitions across cognitive states after age 60. J Intern Med. 2023 Aug;294(2):191-202. doi: 10.1111/joim.13657.

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VI. Tazzeo C, Rizzuto D, Calderón-Larrañaga A, Dekhtyar S, Zucchelli A, **Xia X**, Fratiglioni L, Vetrano DL. Living longer but frailer? Temporal trends in life expectancy and frailty in older Swedish adults. J Gerontol A Biol Sci Med Sci. Accepted.

Contents

1 Introduction 1
1.1 Population aging and the disease burden of dementia 1
1.2 The cognitive continuum of dementia 1
1.3 Cardiovascular health, cardiovascular disease, and dementia 3
1.3.1 The role of cardiovascular health in the cognitive continuum of dementia 3
1.3.2 Cardiovascular diseases and dementia 5
1.4 Orthostatic hypotension and cognitive aging 6
1.4.1 An overview of orthostatic hypotension 6
1.4.2 Orthostatic hypotension and dementia 7
1.4.3 Cardiovascular diseases—a link between orthostatic hypotension and dementia? 7
1.4.4 Frailty, orthostatic hypotension, dementia, and mortality 8
1.5 Knowledge gaps 9
2 Research aims 10
3 Materials and methods 11
3.1 Study design 11
3.1.1 The Swedish National Study on Aging and Care in Kungsholmen 11
3.1.2 Study populations 12
3.2 Assessment of study exposures 14
3.2.1 Life's Simple 7 14
3.2.2 Orthostatic hypotension 15
3.2.3 Frailty 15
3.3 Assessment of study outcomes 16
3.3.1 Cognitive impairment, no dementia 16
3.3.2 Dementia 17
3.3.3 Cardiovascular diseases and death 18
3.4 Assessment of study covariates 18
3.4.1 Demographic, lifestyle, and psychosocial factors 18
3.4.2 Diseases and slow walking speed 19
3.4.3 *APOE* genotyping 19
3.5 Statistical analyses 19
3.5.1 Continuous-time multistate model, transition probability, and length of stay 22
3.5.2 Flexible parametric survival model and standardized cumulative incidence 23
3.5.3 Missing data 23
3.6 Ethical considerations 25
4 Results 26
4.1 Characteristics of the study populations 26
4.2 Associations of LS7 with CIND, dementia, and life years in normal cognition (*Study I*) 26

4.3 Associations of OH with CIND and dementia (*Study II*) ... 27
4.4 Associations between OH and CVD and dementia (*Study III*) ... 29
4.5 Associations of OH and frailty with dementia and death (*Study IV*) ... 29
5 Discussion ... 32
5.1 Main findings ... 33
5.2 Interpretations of the main findings ... 33
5.2.1 Life's Simple 7 and cognitive aging ... 33
5.2.2 Orthostatic hypotension and cognitive aging ... 34
5.3 Methodological considerations ... 36
5.3.1 Selection bias ... 37
5.3.2 Measurement error ... 37
5.3.3 Confounding bias ... 39
5.3.4 Generalizability ... 40
6 Conclusions ... 40
7 Points of perspective ... 41
7.1 Implications of the study findings ... 41
7.2 Future directions ... 42
8 Acknowledgements ... 43
9 References ... 46
10 Appendix ... 61

List of abbreviations

AD	Alzheimer's disease
AHA	American Heart Association
APOE	Apolipoprotein E
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BP	Blood pressure
CDR	Cause of Death Register
CIND	Cognitive impairment, no dementia
CI	Confidence interval
CVD	Cardiovascular disease
CVF	Cardiovascular risk factor
CVH	Cardiovascular health
DBP	Diastolic blood pressure
HbA1c	Glycated hemoglobin A1c
HR	Hazard ratio
ICD	International Classification of Diseases
LS7	Life's Simple 7
MCI	Mild cognitive impairment
NPR	National Patient Register
OH	Orthostatic hypotension
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SBP	Systolic blood pressure
TIA	Transient ischemic attack

1 Introduction

1.1 Population aging and the disease burden of dementia

The percentage of people aged ≥60 years worldwide was 13.5% in 2020 and is predicted to be 20% by 2050 (1). In addition, the number of persons aged ≥80 years worldwide is estimated to triple between 2020 and 2050 (2). The rising percentage of older adults within the global population necessitates more research and actional plans for offering sustainable healthcare to this population and promoting healthy aging, defined by the World Health Organization as the development and maintenance of functional abilities that are essential for well-being in old age (1).

Dementia is a clinical syndrome characterized by cognitive impairment that is severe enough to interfere with daily activities and is a significant barrier to healthy aging (3). Dementia leads to an excessive mortality rate and is the fourth greatest contributor to disability-adjusted life years in persons aged 75 years and older globally (4). With population aging being one of the main drivers of increases in dementia prevalence, the number of people with dementia is predicted to increase globally from 57 million in 2019 to 153 million in 2050 (5). In Sweden, the setting of this thesis, the number of people with dementia is forecasted to increase from approximately 150,000 in 2019 to 250,000 in 2050 (5).

Dementia not only hinders healthy aging for individuals but also poses immense burdens for the patients' families and society (6, 7). Caregivers of dementia patients are more likely to develop mental and physical disorders than non-dementia caregivers (6). The annual costs of dementia per person (indirect costs, direct medical costs, and direct social costs) worldwide were about 24,000 US dollars in 2019, with informal care costs accounting for 50% of the costs (7). In Nordic European countries, the annual costs of dementia per person were about 43,767 euros in 2021 (8).

Treatment of dementia is mainly symptomatic at present. There have been important advances in the development of treatments capable of altering the disease course in recent years (9, 10). However, such treatments mainly target Alzheimer's disease (AD), the most common cause among several causes of dementia, with moderate clinical benefits and uncertain benefit-risk profiles (11-13). On the other hand, a previous study showed that up to 40% of dementia cases worldwide could be attributed to twelve modifiable risk factors (14); thus, dementia prevention via modifying these risk factors may be an effective way to combat the increasing burden of dementia.

1.2 The cognitive continuum of dementia

Dementia is a clinical syndrome with heterogeneous underlying neuropathology (15). AD, characterized by extracellular β-amyloid plaques (abnormally aggregated β-amyloid protein) and intracellular neurofibrillary tangles (abnormally aggregated hyperphosphorylated tau protein), accounts for 60-80% of dementia cases (16).

Vascular dementia is caused by diseases of large or small blood vessels and, alone or combined with AD, accounts for 20–30% of dementia cases (16). Other types of dementia include, among others, dementia with Lewy bodies and frontotemporal dementia (16). More than half of the dementia cases in older adults have mixed brain pathologies, with AD and vascular pathologies being the most common combination (17–21). The pathological process of dementia can start decades before the occurrence of severe cognitive impairment. People who are later diagnosed with dementia typically have normal cognition in the early stage of the disease (22, 23). Therefore, dementia is better understood as a continuum from normal cognition to severe cognitive impairment affecting daily life. Several terms are used to describe the intermediate stage in the cognitive continuum after normal cognition and before the development of overt dementia. Mild cognitive impairment (MCI) and cognitive impairment, no dementia (CIND) are two common terms to represent the intermediate stage between normal cognition and overt dementia in the cognitive continuum (24).

The clinical diagnosis of MCI/CIND and dementia requires information regarding the medical history and cognitive performance as well as a physical examination and laboratory testing (15, 25–27). Typically, multiple cognitive domains are tested, including memory, attention, executive function, language, and visuospatial ability (15, 25). The probable cause of MCI/CIND and dementia can be assessed by recognizing specific clinical phenotypes and with the assistance of *in-vivo* biomarkers (e.g., brain imaging and cerebrospinal fluid biomarkers) (28, 29). The diagnostic criteria for MCI include: (i) a subjective cognitive complaint, (ii) objective cognitive impairment, (iii) preserved independence in activities of daily living, and (iv) the exclusion of dementia (25, 30). Objective cognitive impairment in research settings is usually measured by neuropsychological tests and is defined as scoring 1 or 1.5 standard deviations below the age-specific mean of the scores of the cognitive domains (26). Despite the common goal of CIND and MCI to capture people on the disease course of dementia and the similarities in their diagnostic criteria, there are two major differences in the operationalizations of MCI and CIND in research settings: the diagnosis of CIND does not require (i) a subjective cognitive decline or (ii) the exclusion of functional impairment (27). The operationalization of CIND is preferable in the population-based research setting, as including the two above-mentioned MCI criteria may compromise the sensitivity and specificity of identifying truly affected individuals (26). Therefore, the construct of CIND has been used in the present doctoral project.

The risk of developing MCI syndrome increases with age, with the incidence ranging from 22.5 per 1000 person-years for those aged 75–79 years to 60.1 per 1000 person-years for those aged 85 years and above (31). Notably, not all people with MCI/CIND will eventually develop dementia; instead, they are at a greater risk for developing dementia than people of the same age (32, 33). Furthermore, some people with MCI can revert to normal cognition (33). Approximately 15% of people aged older than 65 years with MCI develop dementia over two years (33), whereas 18% of people with MCI revert to normal cognition (34). However, persons with MCI but later revert to normal cognition have a

higher risk of developing MCI again or developing dementia than those who are not previously diagnosed with MCI (33). The probabilities of reversion and progression of MCI differ significantly across settings, with a higher progression possibility and lower reversion possibility in clinical settings than in community-based settings (34-36).

The nature of MCI reversion to normal cognition is complex. Previous research suggests multiple possible underlying causes, including misclassification of MCI cases due to non-robust diagnostic tools or practice effects, remission of MCI, and actual recovery from MCI (34, 37-39). Identifying predictors of MCI/CIND reversion to normal cognition would improve our understanding of this phenomenon and may be clinically meaningful if the reversibility of MCI is established.

1.3 Cardiovascular health, cardiovascular disease, and dementia

1.3.1 The role of cardiovascular health in the cognitive continuum of dementia

Ageing is a crucial risk factor for cognitive decline and dementia (40, 41). Changes in the brain during aging include but are not limited to cortical thinness, smaller brain volumes, decreased white matter integrity, and changes in brain network connectivity (40). In addition, aging is a crucial risk factor for neurodegenerative diseases, including AD (41). However, previous studies indicate that the development of dementia is also affected by many other factors, including genetic factors (e.g., *APOE* ε4 allele carriership—the strongest genetic risk factor for sporadic AD), environmental factors (e.g., air pollution), psychosocial factors (e.g., social network), and lifestyle factors (e.g., unhealthy diet) (14, 42). Some of these factors can be modified on a societal or individual level, meaning there is a potential for preventing or postponing the onset of dementia by changing those factors.

A body of studies has suggested that conventional cardiovascular risk factors (CVFs, e.g., smoking, hypertension, and diabetes) are related to a higher risk of cognitive decline and dementia in older adults (14, 42-46). The 2020 report of the Lancet Commission on Dementia Prevention, Intervention, and Care suggests that controlling 12 modifiable risk factors, including six CVFs (hypertension, excessive alcohol consumption, obesity, smoking, physical inactivity, and diabetes) may prevent up to 40% of dementia cases worldwide (14).

Similarly, many risk factors for incident MCI in people with normal cognition and progression from MCI to dementia are conventional CVFs, including physical inactivity, smoking, excessive alcohol consumption, overweight/obesity, hypertension, diabetes, and dyslipidemia (42, 47-52). Other factors that increase the likelihood of progression from MCI to dementia include older age, *APOE* ε4 allele carriership, metabolic syndrome, depression, abnormal cerebrospinal fluid biomarkers, poor baseline cognitive performance, and amnestic type of MCI (47, 49, 52-55). On the other hand, a Mediterranean-like diet may protect against the deterioration from normal cognition to MCI and from MCI to dementia (42, 47, 56).

The risk factors for incident MCI in people with normal cognition and progression to dementia in people with MCI are also generally associated with a lower likelihood of MCI reversion to normal cognition (57, 58). In addition, people having no history of stroke seem to have a higher likelihood of reverting from MCI to normal cognition (57). Interestingly, previous studies found persons with MCI who reversed to normal cognition had similar likelihood of being *APOE* ε4 allele carriers, cerebrospinal fluid biomarkers, and imaging characteristics to cognitively normal people; however, those who reversed from MCI to normal cognition had a higher ischemic risk than cognitively normal people (37, 59). These findings suggest that cardiovascular health (CVH) may impact the clinical course of MCI.

Consistent with the associations of individual CVFs with MCI and dementia, recent studies have demonstrated that adherence to ideal CVH defined by Life's Simple 7 metrics (LS7) is associated with a decreased risk of dementia in older adults (**Figure 1**) (60-71). LS7 was introduced by the American Heart Association (AHA) in 2010 to define ideal levels for seven well-established CVFs that people should aspire to achieve or manage: current smoking, physical activity, body mass index (BMI), healthy diet, total cholesterol, blood pressure (BP), and fasting plasma glucose (72). However, the associations of ideal CVH, defined by LS7 metrics, with the transitions between normal cognition, CIND, and dementia remain unclear, particularly that of the reversion from CIND to normal cognition. In addition, the negative effects of conventional CVFs on cognition seem to lessen with advanced age, and the clinical implications of conventional CVFs and their ideal levels in very old age (e.g., ≥80 years) are unclear (46, 73-77). For instance, previous studies have shown that BP, BMI, and total cholesterol levels tend to decline progressively before dementia onset and death, meaning lower levels of these factors in very old age may not always reflect ideal CVH (78-81).

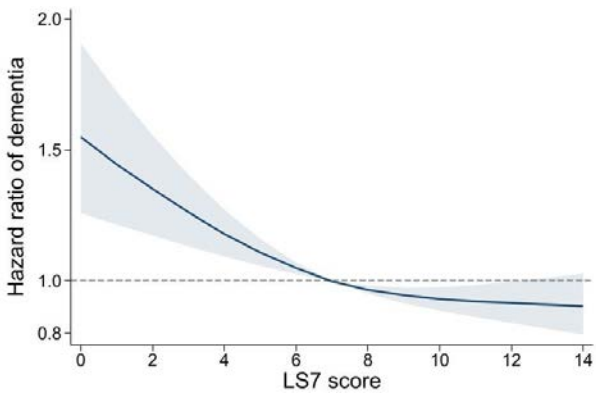

Figure 1. Associations of LS7 score with dementia in people aged ≥65 years from a meta-analysis adapted from *Wu et al. 2022* (71).

The oldest-old adults, inconsistently defined as ≥80, ≥85, or ≥90 years in the literature, is a rapidly growing age group in older adults (2). The oldest-old adults often have very complex subclinical or clinical health conditions, including (i) prevalent neuropathological burdens (e.g., >40% had AD pathologies), (ii) multimorbidity (e.g.,

prevalence >80%), (iii) frailty (prevalence >30%), and (iv) polypharmacy (e.g., 30-70% taking ≥6 medications) (74, 75, 82-84). In addition, in the "oldest-old", non-AD pathologies (e.g., microinfarcts, TDP-43) seem to play a major role in the development of dementia, suggesting that dementia in the oldest-old adults may have a different pathological basis than in younger old adults (75, 85). All these conditions pose challenges to the relevance and feasibility of the ideal CVH goals set out by LS7 in the oldest-old adults. Nevertheless, the associations between LS7 and cognitive transitions in the oldest-old have not been investigated.

1.3.2 Cardiovascular diseases and dementia

Cardiovascular diseases (CVD) are direct clinical manifestations of poor CVH and can mediate the association between CVFs and dementia (86-97). In particular, stroke is a strong risk factor for dementia and is estimated to double the risk of all-cause dementia (86). Compared with the general population, the onset of dementia in stroke survivors is 2 years earlier in those with transient ischemic attack (TIA) and 25 years earlier in those with severe strokes (87). Notably, cognitive impairment can occur before stroke and is associated with an increased risk of post-stroke dementia (88). In addition to stroke, other prevalent CVDs in older adults, including coronary heart disease, atrial fibrillation, and heart failure, can also increase dementia risk (89, 90, 92). Longitudinal studies have shown that people with coronary heart diseases have a 27% increased risk of dementia, and people with congestive heart failure have a 60% increased risk of dementia, and the associations could not be fully explained by confounding CVFs (89). Atrial fibrillation, another common CVD in older adults, was found to be associated with a 38% increased dementia risk (90).

In line with the associations of CVD and dementia, post-mortem neuropathological data have suggested that vascular pathology (e.g., atherosclerosis and cerebral small vessel diseases) might confer a similar risk of dementia as AD pathology (e.g., β-amyloid plaques and neurofibrillary tangles), the most common neurodegenerative disease in older adults; a mix of vascular and AD pathology has been found to almost double the risk of dementia compared with pure AD pathology (98). The vascular pathway is estimated to account for 32% of the age-related dementia risk (99).

In recent decades, age-standardized dementia incidences have declined in high-income countries (100, 101). The declining dementia incidence has been accompanied by lower incidences of ischemic heart disease and stroke (100). Furthermore, a recent study using post-mortem neuropathological data from four birth cohorts between 1905-1930 has shown a decrease in age-standardized atherosclerosis and arteriosclerosis in the brain across the birth cohorts, but there has been no decrease in the neurodegenerative pathological burdens (102). These findings suggest that it is possible to reduce the burden of dementia by reducing the burden of CVDs.

1.4 Orthostatic hypotension and cognitive aging

1.4.1 An overview of orthostatic hypotension

There has been increasing interest in investigating orthostatic hypotension (OH) as a potential risk factor for CVDs and dementia (103–114). OH is a drastic drop in BP when standing up as a result of failed hemodynamic adaptation to the postural change; it is defined as systolic blood pressure (SBP)/diastolic blood pressure (DBP) decreasing ≥20/10 mm Hg within three minutes after standing up from a lying position (115). This definition of OH is usually referred to as classic or consensus OH. Two other common OH subtypes are initial OH (SBP/DBP drops ≥40/20 mm Hg within 30 seconds of standing up) and delayed OH (OH after 3 minutes) (115).

During orthostasis, blood is redistributed to the lower part of the body, and cardiac output is reduced due to decreased venous return to the heart (115). This can lead to a decrease in arterial BP (115). For people with normal physiological adaptations, there are several mechanisms to stabilize postural BP changes (116, 117). When BP drops, the baroreceptors in carotid sinuses and the aortic arch will sense the changes in the stretching of blood vessel walls and reduce firing, which transmits signals through the glossopharyngeal nerve and the vagus nerve and leads to decreased firing of neurons in the caudal ventrolateral medulla and less inhibition of the neurons in the rostral ventrolateral medulla (116, 117). The increased firing of neurons in the rostral ventrolateral medulla finally leads to an increased release of norepinephrine in the postganglionic neurons, which increases vasoconstriction and heart rate, helping to stabilize BP (116, 117). These mechanisms are fast-reacting and happen within seconds. A slower hormonal reaction also helps to stabilize BP by increasing the release of vasopressin from the posterior pituitary, which is mediated by the paraventricular nucleus and supraoptic nucleus in the hypothalamus (116, 117). Vasopressin can increase vasoconstriction and fluid reabsorption in the kidney, which then leads to increased blood volume and stabilizes BP (116, 117).

Many factors can affect the afferent and efferent pathways that control BP stabilization during postural changes and lead to OH. These factors include volume loss (e.g., due to dehydration), hypertension, diabetes, heart failure, neurodegenerative diseases (e.g., Dementia with Lewy bodies, Parkinson's disease, and multiple system atrophy), and use of antihypertensive medications and antidepressants (116, 118, 119). Vascular aging is also a risk factor for OH, as previous studies have shown that higher levels of arterial stiffness, measured by pulse wave velocity, are associated with more significant BP drops during orthostasis and a higher likelihood of OH (120–123). In addition, older adults with OH are more likely to have abnormal nocturnal BP patterns, such as non-dipping and reverse-dipping patterns, which are potential risk factors for CVD (124). Furthermore, a recent study showed that individuals with probable sarcopenia, measured by hand grip strength, had impaired BP recovery during orthostasis, suggesting weak muscle strength is also a risk factor for OH (125). Depending on whether OH is caused by underlying neurological conditions, OH can be divided into non-

neurogenic and neurogenic OH (118). People with neurogenic OH caused by neurodegenerative α-synucleinopathies have blunted heart rate during postural changes; a heart rate increase to SBP decrease ratio <0.5 indicates neurogenic OH (118, 126).

Unsurprisingly, the stabilization of BP during postural changes is slower in older adults than in younger adults. Data from the Irish Longitudinal Study on Ageing indicate that people aged 50-59 years usually have stable BP within 30 seconds of standing, whereas older adults require >30 seconds to stabilize their BP (127). BP response patterns are similar in women and men (127). OH is also common among older people. OH affects 22.2% (95% CI = 17%-28%) of older adults living in communities and 23.9% (95% CI = 18.2%-30.1%) of older adults living in long-term care facilities (128). OH has been related to elevated risk of several adverse health outcomes, including CVDs, dementia, falls, and all-cause mortality (129-131).

1.4.2 Orthostatic hypotension and dementia

While it is well-known that several neurodegenerative diseases can cause OH, there is also evidence suggesting that OH may be a risk factor for dementia (106-114). Previous epidemiological research, mostly conducted in community-dwelling individuals, has indicated that OH is related to a 30% elevated risk of dementia (106-110, 113, 114). The associations between OH and dementia reported by these studies have remained after adjusting for shared risk factors between OH and dementia, such as diabetes and hypertension (107-110, 113).

The mechanisms through which OH can influence dementia development in general populations are not clear. It is postulated that OH can cause hypoperfusion in the brain, which may then lead to ischemic injury and cognitive dysfunction (132-135). In line with this view, previous studies using magnetic resonance imaging data have shown that people with OH have increased burdens of cerebral small vessel diseases, such as more severe white matter hyperintensity burdens and a higher probability of lacunes, which can result from cerebral hypoperfusion and cerebral ischemic injury (136-139). Magnetic resonance imaging markers of cerebral small vessel diseases, especially white matter hyperintensity burden, have been associated with an increased risk of dementia (139-141).

Although previous studies generally suggest that OH is associated with an elevated dementia risk, whether OH is also associated with CIND is unclear. In addition, a study in memory clinic patients showed that OH was predictive of MCI progression to dementia (112), but the results need to be confirmed in population-based studies.

1.4.3 Cardiovascular diseases—a link between orthostatic hypotension and dementia?

Previous studies suggest that people with OH have an elevated risk of several common CVDs in older adults, such as ischemic heart disease, atrial fibrillation, heart failure, and

stroke (103-105). Such associations have been observed in both middle-aged adults and older adults, with no significant effect modifications by age (103-105).

The associations between OH and these CVDs do not seem to be solely driven by shared risk factors. Data from the Atherosclerosis Risk in Communities study showed that OH was related to a higher risk of incident myocardial infarction, heart failure, coronary heart disease, and stroke even after controlling for other CVFs such as intima-media thickness, carotid plaque, and left ventricular hypertrophy (142-144). Similarly, the Cardiovascular Health Study showed that OH was related to a higher risk of incident heart failure after matching 40 baseline characteristics, including CVFs, clinical and subclinical morbidities, use of antihypertensive medications, geriatric parameters, and other factors (145). Furthermore, a study of older adults showed that OH was related to a higher risk of cardiovascular events (cardiovascular death, nonfatal stroke, and myocardial infarction), but reverse dipping, an abnormal circadian BP rhythm that often co-occurs with OH, was not associated with those cardiovascular events (124, 146). These findings suggest that OH may be a potential risk factor for CVDs that commonly affect older adults (i.e., ischemic heart disease, atrial fibrillation, heart failure, and stroke) (147). However, the mechanisms underlying the effects of OH on these CVDs are poorly understood. It is postulated that OH may increase the risk of CVDs by inducing hypoperfusion in the heart, which will then lead to myocardial injury and ischemic events (120, 142, 148).

Given the associations between OH and increased risk of CVDs and that CVDs can increase the risk of dementia, it is plausible to hypothesize that the relationship between OH and dementia in older adults can be partly accounted for by the intermediate development of CVDs (86-97, 103-105). Nevertheless, previous studies have not assessed the relationships between OH and CVDs and dementia simultaneously and have not taken the temporal order between CVDs and dementia into consideration.

1.4.4 Frailty, orthostatic hypotension, dementia, and mortality

Frailty is a common clinical syndrome in older adults defined as a decreased physiological reserve and increased susceptibility to stressors and is predictive of many adverse health outcomes, including falls, hospitalization, and mortality (149). Therefore, frailty has been recommended as a measure of accelerated biological aging in both clinical and research settings (150). The estimated prevalence of frailty ranges from 11% in people aged 50-59 years to 51% in people aged 90 years or older (84). Currently, there is no consensus on how to diagnose frailty. The most commonly used frailty instruments are the frailty phenotype and the frailty index (151, 152). The frailty phenotype model defines frailty as having more than two of the following five conditions: unintentional weight loss, weakness, exhaustion, slowness, and low activity (151). The frailty index is defined as the proportion of health deficits among the total measured potential deficits (e.g., diseases, signs, symptoms, and functional impairments) and ranges between 0–1, with larger values indicating higher levels of frailty (152).

OH is conceptually similar to frailty, as OH can be seen as failed responses of multiple body systems (e.g., cardiovascular system, nervous system) to the stressor of postural changes. Indeed, frailty and autonomic dysfunction, which can lead to OH, often co-occur in older adults (153). Similar to OH, frailty has been associated with a higher risk of dementia in previous studies (154-167). In addition, both OH and frailty have been associated with higher mortality rates (103, 129, 149). Despite the frequent co-occurrence of OH and frailty in older adults and their associations with dementia and mortality, whether OH is associated with dementia and mortality independently of frailty status remains unclear.

1.5 Knowledge gaps

First, existing evidence suggests that maintaining ideal CVH, defined by LS7, can reduce the risk of dementia in old age. However, whether maintaining LS7-defined ideal CVH can protect against CIND and dementia in the oldest old adults is unclear. Second, OH has been associated with an elevated risk of dementia in older adults. Nevertheless, the relation between OH and CIND and the progression from CIND to dementia are unclear. Third, whether the association between OH and dementia is linked via CVDs has yet to be investigated. Fourth, OH and frailty often co-occur in older adults, and both have been associated with elevated dementia risk. Nevertheless, whether OH is associated with dementia independently of frailty status is unknown. Addressing these knowledge gaps can help to establish relevant protective and risk factors for dementia in old age, which may then contribute to the development of dementia prevention strategies in the future.

2 Research aims

The overall aim of the doctoral thesis is to understand the roles of cardiovascular health and orthostatic hypotension in cognitive aging. Specific points of inquiry are investigated in the four individual studies listed below:

Study I. To assess the effects of ideal cardiovascular health on the transitions between cognitive states in older adults.

Study II. To evaluate the association of orthostatic hypotension with the deterioration from normal cognition to dementia in older adults.

Study III. To evaluate the impact of orthostatic hypotension on the development of cardiovascular diseases and subsequent dementia onset.

Study IV. To assess whether orthostatic hypotension is associated with dementia and mortality in the presence and absence of frailty in older adults.

3 Materials and methods

3.1 Study design

The four studies in this thesis are epidemiological studies, which can complement the findings of preclinical research and randomized controlled trials in multiple ways (168). Epidemiological studies can validate the findings from preclinical research using animal models in human populations (168). In addition, observational epidemiological studies can provide evidence and insights when randomized controlled trials are not suitable for certain research questions in human populations due to ethical or practical issues (168).

The four studies were designed as observational population-based cohort studies. This study design was adopted instead of other designs, such as cross-sectional designs, because it provides more certainty regarding the temporality of the study exposure and the study outcome. Another advantage of the cohort study design over other study designs (e.g., case-control study designs) is that the studies in this thesis are based on secondary data (a population-based project in approximately 3000 older adults); a cohort design would make the most of the available information.

3.1.1 The Swedish National Study on Aging and Care in Kungsholmen

The four studies in this thesis used data from the ongoing Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) study (169). The SNAC-K aims to study the aging process and identify factors that can benefit the health and care of older adults (169).

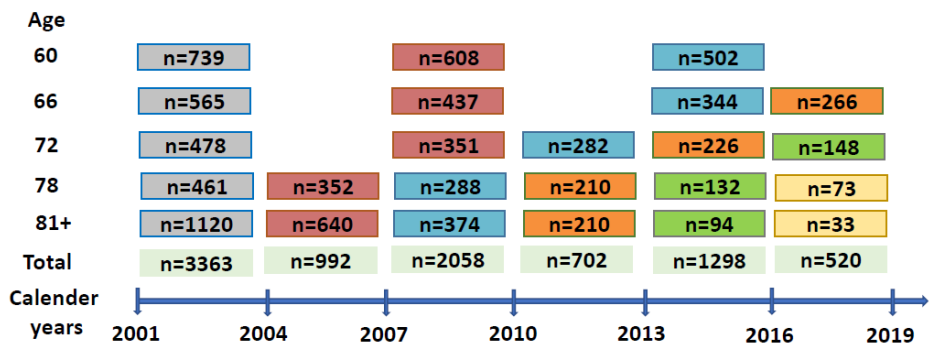

Figure 2. The study population of the SNAC-K study

The SNAC-K applied an age-stratified random sampling strategy to recruit study participants in residents aged 60 years or older living at home or in institutions in a central area of Stockholm, Kungsholmen, from the Swedish Population Register using the personal identity numbers, which are unique for each individual in the register. The SNAC-K selected random samples from eleven age strata: 60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and ≥99 years (**Figure 2**). Among the 5111 individuals in the random sample, 321 were ineligible (deaf, could not speak Swedish, moved, or lacking contact information), and 200 were deceased. Between March 2001 and June 2004, 3363 of the 4590 alive

and eligible individuals took part in the first study examination. Then, participants under 78 years (younger cohorts) were followed every six years, and participants aged 78 years or older (older cohorts) were followed every three years (**Figure 2**). The studies in this thesis used the cohorts initiated from 2001–2004 (baseline) and used the data from baseline to December 2019.

At each study visit, trained staff, including nurses, physicians, and psychologists, collect demographic information and information on lifestyles and evaluate health status through interviews, clinical assessments, and cognitive testing following standardized protocols and procedures. For each study participant, the whole procedure lasts six hours on average. Diseases and symptoms are coded using the International Classification of Diseases 10th Revision (ICD-10) codes. The participants or their caregiver/proxy, if the participants are cognitively impaired, bring a list of currently used medications and containers of medications. For institutionalized participants, medication use is ascertained from medical records. Medication use is recorded using the Anatomical Therapeutic Chemical (ATC) codes.

Additional information on medical conditions is also derived from the Swedish National Patient Register (NPR) and the Swedish Cause of Death Register (CDR), which are linked to the SNAC-K data (170, 171). The NPR was initiated in 1964 and reached national coverage for discharged inpatient care in 1987 (170). In 2001, NPR started covering specialized outpatient care (170). The CDR has registered death dates and causes of death since 1961 (171). The NPR and CDR register diseases and causes of death with ICD codes and are updated monthly and annually, respectively (170, 171).

3.1.2 Study populations

Figure 3 shows the study populations in each of the four individual studies in this thesis. *Study I* included 2746 dementia-free participants for the analyses of the relationship between LS7 and dementia and 2470 participants who had CIND information for the analyses of LS7 in relation to transitions between normal cognition, CIND, and dementia.

Study II included 2532 dementia-free participants for the analyses of OH in relation to dementia, 1535 baseline CIND-free participants for the analyses of OH in relation to CIND, and 576 participants with CIND at baseline for the analyses of OH in relation to CIND progression to dementia.

Study III included 1986 baseline dementia-free and CVD-free participants for the analyses of the relationships between OH and transitions between no CVD, CVD, and dementia and 717 participants who had CVD at baseline for the analyses of the OH-dementia association in people with CVD.

Study IV included 2703 participants initially free of dementia for the analyses of the associations of OH and frailty with dementia and mortality.

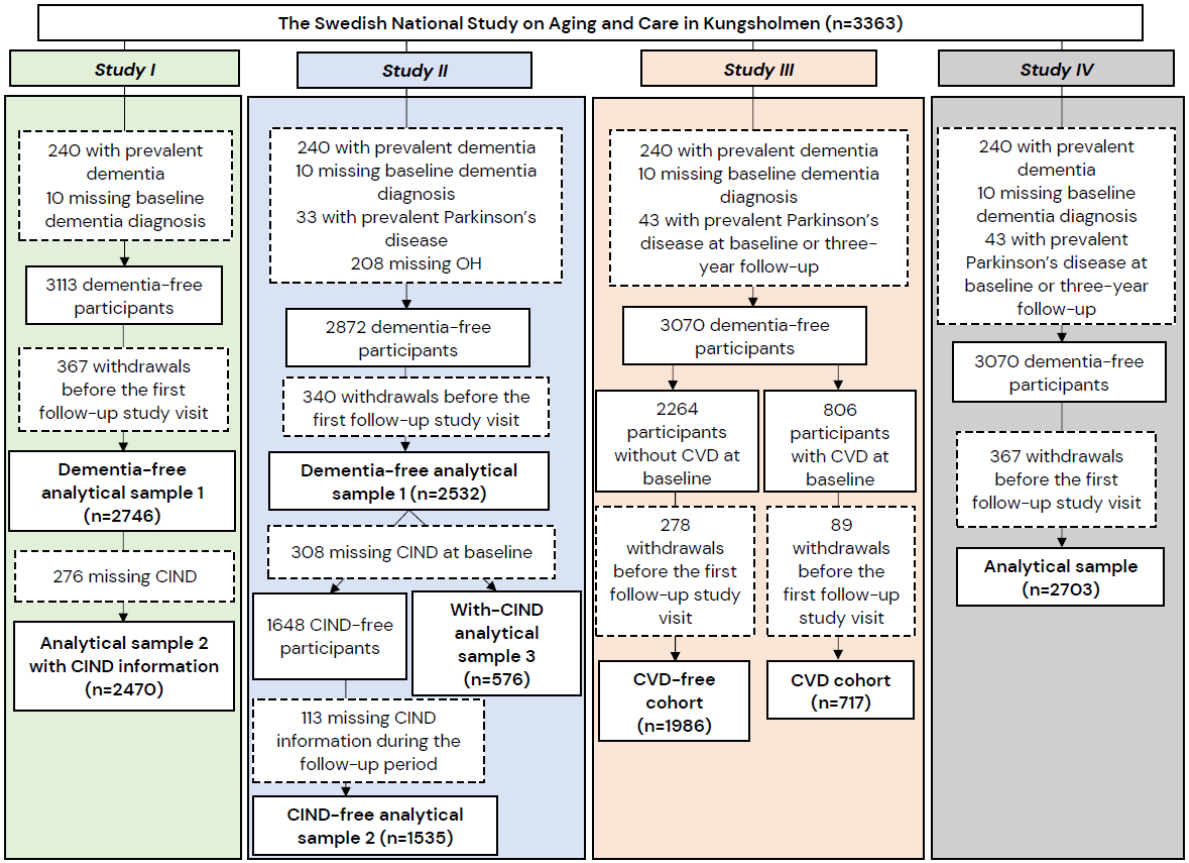

Figure 3. Flowchart of the study populations in the thesis

Abbreviations: CIND = cognitive impairment, no dementia; CVD = cardiovascular disease; OH = orthostatic hypotension.

3.2 Assessment of study exposures

3.2.1 Life's Simple 7

LS7 classifies seven cardiovascular metrics into poor (score = 0), intermediate (score = 1), and ideal CVH (score = 2) levels (**Table 1**). We modified the AHA criteria for physical activity and fasting plasma glucose due to the lack of detailed data on those metrics in the SNAC-K and followed the AHA criteria for other metrics (**Table 1**) (72, 172).

Smoking information was collected in the nurse interview. The weight and height of participants were assessed while they wore lightweight clothing and were not wearing shoes, with BMI computed as the ratio of weight (kg) to the square of height (m^2). Physical activity information was collected through a self-administered questionnaire. Diet was evaluated with a 98-item food frequency questionnaire (173). Peripheral blood samples were collected and measured for total cholesterol, hemoglobin A1c, and other blood biochemistry parameters. BP was assessed twice from the left arm in a quiet room with a constant temperature (174, 175). Each time, sitting BP was measured after a 5-minute rest (174, 175).

LS7 was analyzed as a total LS7 score (range: 0-14) by summarizing the scores of the seven factors and also as a binary variable (better CVH: LS7 score ≥8 versus worse CVH: LS7 score <8) in *Study I*.

Table 1. AHA criteria and operationalization of LS7 in *Study I*

Metric	AHA criteria	Operationalization in *Study I*
Current smoking	**Poor health:** Current smoking; **Intermediate health:** Former ≤12 months; **Ideal health:** Never or quit >12 months	Same as the AHA criteria
Body mass index	**Poor health:** ≥30 kg/m^2; **Intermediate health:** 25-29.9 kg/m^2; **Ideal health:** <25 kg/m^2	Same as the AHA criteria
Physical activity	**Poor health:** None; **Intermediate health:** 1-149 min/week moderate intensity or 1-74 min/week vigorous intensity or 1-149 min/week moderate+vigorous; **Ideal health:** ≥150 min/week moderate intensity or ≥75 min/week vigorous intensity or ≥150 min/week moderate+vigorous	**Poor health:** Never or ≤2-3 times/month light, moderate, or intense exercise; **Intermediate health:** Light exercise several times per week or every day; **Ideal health:** Moderate or intense exercise several times per week or every day
Healthy diet score	**Poor health:** 0-1 components; **Intermediate health:** 2-3 components; **Ideal health:** 4-5 components	Same as the AHA criteria
Total cholesterol	**Poor health:** ≥240 mg/dL; **Intermediate health:** 200-239	Same as the AHA criteria; **ATC codes for medication:** C10

	mg/dL or treated to goal; **Ideal health:** <200 mg/dL	
Blood pressure	**Poor health:** SBP ≥140 or DBP ≥90 mm Hg; **Intermediate health:** SBP 120–139 or DBP 80–89 mm Hg or treated to goal; **Ideal health:** SBP/DBP <120/80 mm Hg	Same as the AHA criteria; **ATC codes for medication:** C02, C03, C04, C07, C08, and C09
Fasting plasma glucose	**Poor health:** ≥126 mg/dL; **Intermediate health:** 100–125 mg/dL or treated to goal; **Ideal health:** <100 mg/dL	**Poor health:** HbA1c ≥6.5%; **Intermediate health:** HbA1c of ≥5.7% to 6.4% or treated to <5.7%; **Ideal health:** HbA1c <5.7% without use of antidiabetic medication; **ATC codes for medication:** A10

Abbreviations: AHA = American Heart Association; ATC = Anatomical Therapeutic Chemical; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; LS7 = Life's Simple 7; SBP = systolic blood pressure. Healthy diet scores include 5 components: high consumption of fruit and vegetables, high consumption of fish, high consumption of fiber-rich whole grains, restricted salt intake, and restricted consumption of sugar-sweetened drinks.

3.2.2 Orthostatic hypotension

Trained physicians manually measured supine BP with a sphygmomanometer after the participants rested for five minutes (174, 175). Participants then stood up, and BP was measured after one minute of standing (174, 175). Physicians asked if the participants experienced any symptoms after one minute of standing and recorded the symptoms using ICD-10 codes. OH was defined as a decline of SBP≥20 mm Hg or DBP ≥10 mm Hg after one minute of standing up (174, 175). In *Study II*, we additionally defined symptomatic OH as having OH and experiencing any of the following symptoms when standing up: dizziness, syncope, fatigue, weakness, and balance disturbances. In *Studies II and III*, we also dichotomized OH into non-neurogenic and neurogenic OH, with the latter defined as a heart rate increase to SBP decrease ratio <0.5 bpm/mm Hg at one minute after standing up (126, 174, 175).

The OH measurement is a part of interviews and examinations performed by physicians, which usually take place between 9:00 and 16:00. Participants typically eat their breakfast or other meals before their study appointments. OH is always measured after the majority of the physician interviews and examinations are done. The time of OH measurement is most often not affected by cognitive status. In some cases, participants ask for very early study appointments. These participants are almost always cognitively intact.

3.2.3 Frailty

Frailty status in *Study IV* was ascertained according to Fried's frailty phenotype criteria (151, 176). The operationalization of the frailty phenotype criteria in *Study IV* is described in **Table 2**. Individuals with 1–2 of the conditions in **Table 2** are deemed pre-frail, and

those having 3–5 conditions are deemed frail (151, 176). In *Study IV*, pre-frailty and frailty were grouped together due to the limited number of people with pure frailty.

Table 2. Fried's frailty phenotype criteria and operationalizations in *Study IV*

Fried's phenotype	Operationalization in *Study IV*
Unintentional weight loss	Weight loss was ascertained through interviews by nurses, and unintentional weight loss was defined as losing ≥1 kg in the last 3 months.
Weak grip strength	The grip strengths of both hands were assessed with an electronic dynamometer under the instruction of trained nurses, and the stronger grip strength value was used. Weak grip strength was defined as the lowest 20% sex-and-body mass index adjusted grip strength of the participants. For participants without a grip strength assessment, weak grip strength was defined as being incapable of opening jars with lids.
Self-reported exhaustion	Self-reported exhaustion was defined as feeling fatigued in the last 3 months.
Slow walking speed	Walking speed was measured through a 6-meter or 2.4-meter walk test, and slow walking speed was defined as the slowest 20% sex-and-height adjusted walking speed of the participants.
Low physical activity level	Physical activity was assessed through a self-administered questionnaire, and low physical activity level was defined as exercising three times per month or less.

3.3 Assessment of study outcomes

3.3.1 Cognitive impairment, no dementia

Cognitive testing for each individual was performed by trained psychologists with a comprehensive neuropsychological battery testing five cognitive domains: episodic memory, executive function, language, visuospatial ability, and perceptual speed (**Table 3**) (177). The whole cognitive testing took about 1.5 hours to complete.

For cognitive domains involving more than one cognitive test, the average of the z-standardized test scores was used as the score for that cognitive domain (177). Cognitive impairment in each cognitive domain was defined as ≥1.5 standard deviations below the age group-specific means (177). CIND was defined as having cognitive impairment in one or more cognitive domains but not meeting the diagnostic criteria for dementia (177). The cognitive tests used for defining CIND were not used for diagnosing dementia, and vice versa.

Table 3. Cognitive tests performed to define CIND in *Studies I and II*

Cognitive domain in CIND	Cognitive test	Description	Scoring
Episodic memory	Free recall	A list of 16 unrelated nouns is presented to the participant every 5 seconds. After the word list, the participants recall the words within 2 minutes.	Number of correctly recalled words.
Executive function	Trail-making test, part B	The participants draw lines to connect circles of numbers and letters in an ascending numeric and alphabetic order.	Number of correct connections.
Language	Category fluency	The participants generate as many words belonging to the categories "animals" and "professions" as possible in 60 seconds.	Mean number of words generated.
	Letter fluency	The participants generate as many words starting with the letters "F" and "A" as possible in 60 seconds.	Mean number of words generated.
Visuospatial ability	Mental rotations	The participants choose a rotated 3D figure out of 3 figures to find the one corresponding to the target 3D figure.	Number of correctly selected figures.
Perceptual speed	Digit cancellation	The participants mark the number "4" in 11 rows of random numbers within 30 seconds.	Number of correctly marked number "4".
	Pattern comparison	The participants mark pairs of line figures as same or different within 30 seconds.	Mean number of correctly marked pairs across 2 trials.

3.3.2 Dementia

The clinical diagnosis of dementia was done following the Diagnostic and Statistical Manual of Mental Disorders-fourth edition criteria (178). The diagnosis of dementia requires (i) the presence of memory impairment, (ii) the presence of one or more of the following disorders: aphasia, apraxia, agnosia, and disturbance in executive function, (iii) the presence of a significant social or occupational functional impairment, and (iv) the impairments do not occur exclusively during delirium (15).

A three-step procedure was adopted for the diagnosis of dementia. A SNAC-K physician made the first diagnoses based on (i) structured interviews regarding medical histories and medication use, (ii) clinical and neurological examinations (e.g., examinations for Parkinson's disease and parkinsonism), (iii) cognitive testing, which included the mini-mental state examination (MMSE), the clock-drawing test, items regarding memory, executive functioning, orientation, problem-solving, and proverb interpretation, and a short story assessing the function of the frontal lobe, and (iv)

evaluations of activities of daily living and instrumental activities of daily living with the participants or their caregivers/proxies if the participant had an MMSE score <24 or was suspected of having dementia (175). Then, another physician made the secondary diagnosis based on the records of the above-mentioned interviews and examinations (175). A neurologist who was not involved in the data collection made the final diagnosis when there was a disagreement between the first and the second diagnoses (175).

Some individuals died between sequential study visits without prior dementia diagnoses. For those people, dementia status was (i) ascertained by a physician by reviewing medical charts and (ii) identified from the Swedish CDR using ICD-10 codes (F00, F01, F02, F03, and G30).

AD was investigated in *Study II* and was clinically diagnosed according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association) criteria (179). Other subtypes of dementia were not investigated in the studies in this thesis due to the limited number of cases. However, they were also clinically diagnosed in the SNAC-K according to commonly used criteria based on the clinical manifestations and temporal course of dementia. Vascular dementia was diagnosed following the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (180). Dementia with Lewy bodies was diagnosed according to the criteria by the Dementia with Lewy Body Consortium (181). Frontotemporal dementia was diagnosed following modified Lund-Manchester criteria (182).

3.3.3 Cardiovascular diseases and death

Ischemic heart disease, atrial fibrillation, heart failure, stroke, and TIA were analyzed as study outcomes in *Study III* and covariates in other studies in this thesis. In *Study III*, the occurrence of CVD was defined as the development of any of the above-mentioned CVDs (175). In addition, ischemic heart disease, atrial fibrillation, and heart failure were grouped as heart diseases and analyzed separately from stroke/TIA in *Study III* (175). The presence and the onset times of CVDs were confirmed by physicians by interviewing medical histories, reviewing medical journals, and reviewing the current use of medications as well as identified from the Swedish NPR using ICD-9 and ICD-10 codes (147, 175). Previous validation studies have shown that the NPR has a good sensitivity for identifying the CVDs studied in this thesis (183-188). Vital status and dates of death were ascertained from the Swedish CDR and by the SNAC-K data collection staff (after 2017).

3.4 Assessment of study covariates

3.4.1 Demographic, lifestyle, and psychosocial factors

Age, sex, highest attained education level, and alcohol consumption were ascertained by trained nurses through interviews. Education level was divided into below high school

level and high school level or above in *Study II* and categorized into elementary, high school, and university levels in *Studies I, III, and IV*.

Interview questions regarding alcohol consumption included: (i) "How often do you drink alcohol?" and (ii) "How many glasses do you drink on a typical day of drinking alcohol?". Heavy alcohol drinking was defined in *Study II* as having ≥8 drinks/week and ≥15 drinks/week for females and males, respectively (174). Physical inactivity was defined in *Study II* as engaging in light, moderate, or intensive exercise ≤2-3 times/month (174). BMI in *Studies III and IV* was divided into four categories: underweight (below 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (30 kg/m^2 and above) (189).

Social network was a composite variable in *Study I* and included several indicators from two dimensions: network size (e.g., number of people to contacts, marital status) and network support (e.g., satisfaction with contacts) (172, 190). The indicators were assessed in nurse interviews and z-standardized and averaged into a total social network score, which was analyzed as a continuous variable in *Study I* (172, 190).

3.4.2 Diseases and slow walking speed

In *Studies II-IV*, hypertension was defined as SBP/DBP ≥140/90 mm Hg or taking antihypertensive medications (ATC codes: C02, C03, C04, C07, C08, and C09); diabetes was defined as glycated hemoglobin ≥6.5%, a record of diabetes in the NPR, or taking antidiabetic medications (ATC code: A10); Parkinson's disease was ascertained by physicians through reviewing medical journals and clinical examinations and from the NPR (ICD-10 codes: G20, G21, G22, G23) (147, 174, 175). In *Study II*, high cholesterol level was defined as total cholesterol ≥6.22 mmol/L or taking lipid-lowering drugs (ATC code: C10) (174). Walking speed was measured through a 6-meter walk test or a 2.4-meter walk test if the participant was unable to complete the 6-meter walk test. In *Study II*, slow walking speed was defined as <0.8 meters/second (174, 191).

3.4.3 *APOE* genotyping

DNA was extracted from peripheral blood samples, and *APOE* genotyping was conducted using matrix-assisted laser desorption/ionization time-of-flight analysis on a modified Sequenom MassARRAY platform at Karolinska Institutet. In *Studies I* and *II*, we dichotomized *APOE* genotype into *APOE* ε4 non-carriers and carriers (172, 174).

3.5 Statistical analyses

The characteristics of the study populations were described using means and standard deviations for continuous characteristic variables (e.g., age) and frequency and proportions for categorical characteristic variables (e.g., education). The characteristics of the study participants by exposure groups (e.g., people with versus without OH) were compared using logistic regressions.

The associations between the exposure variables and the study outcomes were assessed with multistate models and survival analyses (192–194). An overview of the statistical analyses in this thesis is shown in **Table 4** (172, 174, 175). In *Study IV*, we tested the interaction between OH and frailty on the multiplicative scale by including an interaction term between OH and frailty in the statistical models and on the additive scale by calculating relative excess risk due to interaction (195). Missing data in the exposure variables and covariates were addressed with multiple imputation (196). The rationales for choosing these statistical methods are described below.

Table 4. Overview of the statistical analyses in this thesis

Study	Exposure	Outcome and follow-up period	Potential confounders	Statistical analyses and packages
Study I	LS7	CIND, dementia; followed up from 2001-2004 to 2016-2019	Age, sex, education, and social network scores	Multistate models and predictions of lengths of stay ("msm" and "elect" in R); analyses were conducted in the whole study population and then stratified by age (<78 and ≥78 years)
Study II	OH (also divided into symptomatic and asymptomatic OH and neurogenic and non-neurogenic OH)	CIND, dementia; followed up from 2001-2004 to 2013-2016 (a 3-year lag period after baseline was introduced in a sensitivity analysis)	Age, sex, education, BMI, smoking, heavy alcohol drinking, physical inactivity, diabetes, high cholesterol level, SBP in the sitting position, antihypertensive medication use, slow walking speed, number of heart diseases, and cerebrovascular disease	Flexible parametric survival models and predictions of standardized cumulative incidences ("stpm2" and "standsurv" in Stata)
Study III	OH (also divided into neurogenic and non-neurogenic OH)	CVD (also divided into heart diseases and stroke/TIA), dementia; followed up from 2001-2004 to 2016-2019	Age, sex, education, BMI categories, current smoking, hypertension, and diabetes	Multistate Cox survival models ("stmerlin" in Stata)
Study IV	OH, frailty (effect-modifier)	Dementia, death; followed up from 2001-2004 to 2016-2019	Age, sex, education, smoking status, BMI categories, hypertension, diabetes, atrial fibrillation, ischemic heart disease, heart failure, and cerebrovascular disease	Parametric multistate survival models and predictions of standardized cumulative incidences and conditional transition probabilities ("stmerlin", "predictms" "stpm2", and "standsurv" in Stata)

Abbreviations: BMI = body mass index; CIND = cognitive impairment, no dementia; CVD = cardiovascular disease; LS7 = Life's Simple 7; OH = orthostatic hypotension; SBP = systolic blood pressure; TIA = transient ischemic attack.

3.5.1 Continuous-time multistate model, transition probability, and length of stay

Continuous-time multistate models can estimate the transition intensities governing transitions from one state to another and the effects of covariates on the transition intensities by calculating ratios of transition intensities (192, 193). This model framework is useful when there are more than one time-to-event type outcomes of interest and was therefore used in *Studies I, III, and IV*.

The interpretation of the ratios of transition intensities (**Equation 1**) in *Studies I, III, and IV* is similar to the ratios of cause-specific hazards (**Equation 2**) that were estimated with flexible parametric survival models in *Study II* (192–194). In Equation 1, q_{rs} denotes the transition intensity for the transition from the state *r* to the state *s* at time *t*; *S(t)* denotes the state an individual is in at time *t*; δt denotes the time elapsed since time *t* (192). In Equation 2, λ_k^{cs} denotes the cause-specific hazard of event *k* at time *t*; *T* denotes the event time; and *D* denotes the event that occurred (194). The major difference is that the transition intensity is an instantaneous risk of being in a state s at time $t + \delta t$, provided being in a state *r* at time *t*, whereas the cause-specific hazard is an instantaneous risk of an event *k* occurring during the time between *t* and $t + \delta t$, provided being free of any event of interest until time *t*. We dealt with competing events (e.g., death) by estimating such cause-specific hazard ratios (HR) by right censoring the competing events and controlling for factors that may affect both the main outcome and the competing event (197).

$$q_{rs}(t) = \lim_{\delta t \to 0} \frac{P(S(t+\delta t)=s | S(t)=r)}{\delta t} \text{ (Equation 1)}$$

$$\lambda_k^{cs}(t) = \lim_{\delta t \to 0} \frac{P(t \le T < t+\delta t, D=k | T \ge t)}{\delta t} \text{ (Equation 2)}$$

In addition to HRs, which are a relative associational measure, we also estimated conditional transition probabilities in *Study IV* and lengths of stay in *Study I* to better demonstrate the impact of OH and LS7 on cognitive outcomes. Conditional predictions instead of marginal predictions were conducted due to the long computation time of marginal predictions. The hazards and HRs estimated from the multistate models can be integrated into transition probabilities P_{rs}, which mean "given being in the state *r* at a certain time point *u*, the probability of being in the state *s* at a time after that time point *u+t*" (192). Lengths of stay can then be estimated with transition probabilities by integrating over time (**Equation 3**) (198). Notably, there may be more transitions than the direct transition between two states that will contribute to transition probabilities. For instance, in **Figure 4**, the transition probability of death (estimated in *Study IV*) will incorporate (i) the transition intensity from no dementia to death and (ii) the transition intensity from dementia to death.

$$L_s = \int_{t_1}^{t_2} P(t)_{r,s} dt \text{ (Equation 3)}$$

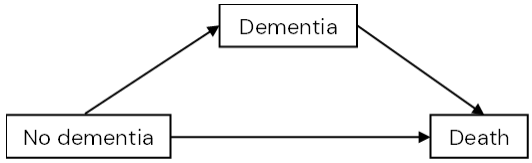

Figure 4. The three-state multistate model in *Study IV*

3.5.2 Flexible parametric survival model and standardized cumulative incidence

In *Studies II* and *IV*, we conducted flexible parametric survival analyses. The major advantage of flexible parametric survival models over the well-known Cox survival model is their ability to model the baseline cumulative hazard using cubic splines. In addition, modelling the baseline cumulative hazard with splines does not assume a specific distribution of the cumulative hazard, thus offering more flexibility.

After fitting the flexible parametric survival models, cumulative incidences of the outcomes of interest can be predicted (**Equation 4**) (194). *S(t)* denotes overall survival, meaning survival from all events when there is more than one event of interest (e.g., when there is a competing event).

$F_k(t) = \int_0^t S(u)\, \lambda_k^{cs}(u) du$ (**Equation 4**)

In *Studies II* and *IV*, we predicted standardized cumulative incidences, which can facilitate the comparisons of cumulative incidences in different groups by forcing the distributions of the covariates to be the same across the groups of varying exposure statuses that are contrasted (194). This is done by specifying the values of the variables that are included in the survival models to their observed values except for the exposure of interest. For instance, in *Study IV*, the standardized cumulative incidence of dementia in robust people without OH was predicted by first predicting the cumulative incidence of dementia for every individual in the study while specifying the OH and frailty status as "robust and without OH" and other variables as their observed values. Then, the predicted cumulative incidences of dementia in all individuals were averaged. The resulting average value would be the standardized cumulative incidence of dementia for robust people without OH.

3.5.3 Missing data

In all studies in this doctoral thesis, there were missing data in the exposure variables and covariates. We dealt with missing data through the multiple imputation approach under the assumption that the data were missing at random (196).

There are three basic missing data assumptions that are important to consider: missing completely at random, missing at random, and missing not at random (196). Missing completely at random means missingness does not depend on the data, observed or unobserved (196). Missing at random means the missing data mechanism is only related to the observed data but not related to the unobserved data (196). Missing not at random means missingness depends on the unobserved data (196). When data are

missing completely at random, complete case analysis (remove the individuals with missingness in any of the variables that will be included in the analysis) usually provides unbiased results. However, complete case analysis can still result in sparse data bias (199). In addition, missing at random is more plausible than missing completely at random in the field of gerontology. When data are missing at random, biases can arise in complete case analysis. **Figure 5** shows a simplified example where the association between OH and dementia could be biased in complete case analysis when there is missing data. Complete case analysis conditions on the missingness status (i.e., no missingness) and opens the pathway *orthostatic hypotension ← age → missingness ←comorbidities → dementia*. Adjustment for variables that lead to dependence between missingness and the outcome may reduce the bias but cannot help with the loss of statistical power. For these reasons, we chose the multiple imputation approach to deal with missing data. More specifically, we chose multiple imputation by chained equation, considering its ability to impute different types of data (196).

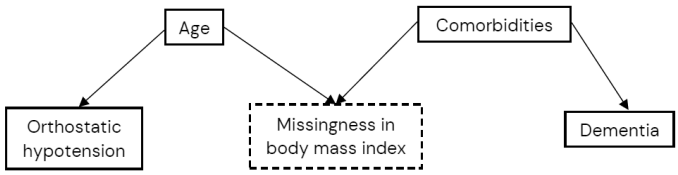

Figure 5. An illustration of missing at random

We applied the multiple imputation by chained equation approach following a standard procedure, which can typically be divided into three steps (196). The first step was to impute missing values with values predicted by observed variables (196). This was done multiple times, and consequently, multiple imputed datasets were generated (196). For this step, we included all variables that would be included in the analytical models in the imputation models; binary variables, categorical variables, and continuous variables were imputed with logistic regression, ordered logistic regressions, and predictive mean matching, respectively. If the analytical models included interactions between covariates (e.g., interaction between OH and frailty in *Study IV*), we also included the interaction terms in the imputation models. We performed 20 imputations for each study in the thesis except for *Study I*, in which only 5 imputations were done considering the long computation time of the multistate models. The second step was to run the analytical model in each imputed dataset (196). The final step was to pool the results of the analyses in each imputed dataset using Rubin's rules (196).

3.6 Ethical considerations

Each study in this doctoral project used data from the SNAC-K. The SNAC-K project and the linkage of SNAC-K data to the Swedish NPR and CDR data were approved by the Regional Ethical Review Board in Stockholm, Sweden (registration numbers: KI 01-114 (baseline), 04-929/3 (1st follow-up), Ö26-2007 (2nd follow-up), 2009/595-32 (register data), 2010/447-31/2 (3rd follow-up), 2013/828-31/3 (4th follow-up), and 2016/730-31/1 (5th follow-up)).

Eligible individuals for the SNAC-K project received an information letter including information on the purpose of the SNAC-K project, a general description of how the study would be conducted, potential risks and benefits, and how personal data would be handled; they then decided whether or not to participate in the research project. Written informed consent was obtained from all participants of the SNAC-K. If the participant was cognitively impaired, a written informed consent was obtained from a proxy. Nurses in the SNAC-K team confirm participation and schedule study visits by phone calls. During each wave of examinations in the SNAC-K, physicians, nurses, and psychologists will collect data through interviews, questionnaires, clinical examinations, laboratory tests, and cognitive tests in a safe and friendly environment. If participants experience any anguish or discomfort in the interview or examination, the procedure is stopped regardless of whether participants provided consent. In the case of abnormal examination results, participants are informed and recommended to be referred to their physicians. The results of the examinations are sent to the participants if requested. Researchers can gain access to the anonymized data from the SNAC-K when the SNAC-K steering group approves the application. It is impossible to trace the information back to a particular individual. Participants can access the research findings from the SNAC-K project via seminars organized by the SNAC-K team and popular science articles. All SNAC-K staff and researchers using the SNAC-K data follow the ethical principles in the World Medical Association Declaration of Helsinki.

4 Results

4.1 Characteristics of the study populations

At baseline (2001–2004), 240 people were diagnosed with dementia, and 10 people had a missing dementia diagnosis. Of the 3113 people free of dementia at baseline, 367 people (228 people from the younger cohorts and 139 from the older cohorts) withdrew before the first follow-up study visit. Of the remaining 2746 people, the mean age was 73.8 (SD, 10.7) years, 1738 (63.3%) people were female, 1370 (49.9%) and 942 (34.3%) people had high school level and university level as highest attained educational levels, respectively, 2042 (74.4%) people had hypertension, 1135 (41.3%) people were taking antihypertensive medication, 255 (9.3%) people had diabetes, 254 (9.2%) people had atrial fibrillation, 406 (14.8%) people had ischemic heart disease, 268 (9.8%) people had heart failure, 190 (6.9%) people had cerebrovascular diseases, 237 (8.6%) people had depression and other mood disorders, 231 (8.4%) people were taking antidepressants, and 688 (25.1%) people had slow walking speed (<0.8 meters/second).

The characteristics of the study populations in the individual studies are described in the corresponding articles and may vary due to differences in study populations and operationalizations of characteristic factors.

The key findings of the individual studies are summarized below. Full results of the studies can be found in the constituting papers and the manuscript (172, 174, 175).

4.2 Associations of LS7 with CIND, dementia, and life years in normal cognition (*Study I*)

In people who initially did not have dementia, a higher LS7 score was associated with a decreased adjusted hazard for dementia in people <78 years (HR = 0.87, 95% CI = 0.78–0.97) but not in people ≥78 years (HR = 1.04, 95% CI = 0.97–1.13) (172). The association between LS7 score and dementia was comparable in *APOE* ε4 allele carriers (HR = 0.88, 95% CI = 0.74–1.04) and non-carriers (HR = 0.87, 95% CI = 0.73–1.04) (172).

In people who did not have dementia and had CIND information during the follow-up period, better CVH (LS7 score ≥8) was related to a lower hazard of incident CIND (HR = 0.76, 95% CI = 0.61–0.95) in individuals under 78 years (172). A higher LS7 score (HR = 0.81, 95% CI = 0.67–0.98) and better CVH (HR = 0.42, 95% CI = 0.21–0.82) were also associated with lower hazards of transitioning directly from normal cognition to dementia in people under 78 years (172). LS7 scores and better CVH were not associated with the reversion of CIND to normal cognition and conversion of CIND to dementia (172). In individuals aged 78 years or above, LS7 scores and better CVH were not related to transitions between the cognitive states (172).

Compared with people with worse CVH, people with better CVH had longer overall survival times (the sum of lengths of stay in all cognitive states) and longer survival times in normal cognition (the length of stay in normal cognition) (**Figure 6**) (172).

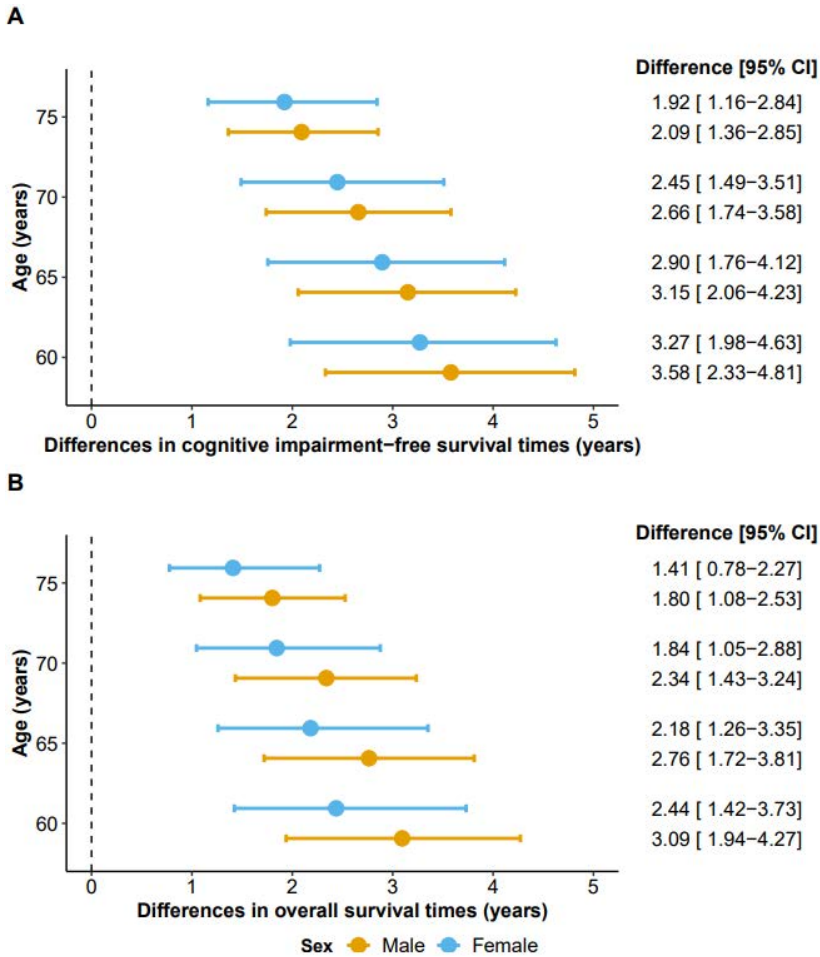

Figure 6. Differences in survival times in normal cognition (A) and overall survival times (B) at ages 60, 65, 70, and 75 years, comparing people with better versus worse cardiovascular health from *Xia et al. 2023* (172).

4.3 Associations of OH with CIND and dementia (*Study II*)

At baseline, 615 (24.3%) people had OH, and 70 people experienced symptoms related to OH (174). The prevalence of OH was 21.6% and 25.7% in people without and with CIND at baseline, respectively (174). Characteristics associated with an increased likelihood of OH included older age, lower BMI, diabetes, lower SBP, slow walking speed, and multiple heart diseases (174).

OH was associated with higher hazards of dementia (HR = 1.40, 95% CI = 1.10–1.76) and AD (HR = 1.39, 95% CI = 1.04–1.86) after adjusting for demographic factors, vascular risk factors, slow walking speed, and prevalent CVDs (**Table 5**) (174). The associations of OH with dementia (HR = 1.40, 95% CI = 1.07–1.82) and AD (HR = 1.39, 95% CI = 1.01–1.89) remained after setting a 3-year lag period following the OH measurement (174). OH was

not associated with incident CIND (HR = 1.15, 95% CI = 0.94–1.40) but was associated with CIND progression to dementia (HR = 1.54, 95% CI = 1.05–2.25) (**Table 5**) (174).

Table 5. Associations of OH with the study outcomes

Analytical samples	Study outcome	No. of cases	HR (95% CI)
2532 people free of dementia at baseline	Incident dementia	322	1.40 (1.10–1.76)
	Incident AD	211	1.39 (1.04–1.86)
1535 people free of CIND at baseline	Incident CIND	546	1.15 (0.94–1.40)
576 people with CIND at baseline	Incident dementia	127	1.54 (1.05–2.25)
	Incident AD	83	1.72 (1.08–2.74)

Models were adjusted for age, sex, education, body mass index, ever smoking, heavy alcohol drinking, physical inactivity, diabetes, high cholesterol level, systolic blood pressure, use of antihypertensive medication, slow walking speed, number of heart diseases, and cerebrovascular disease. Abbreviations: AD = Alzheimer's disease; CIND = cognitive impairment, no dementia; OH = orthostatic hypotension.

The standardized cumulative incidence of dementia was higher in individuals with OH than individuals without OH in those who were initially free of dementia (**Figure 7A**) and in those who had CIND at baseline (**Figure 7B**).

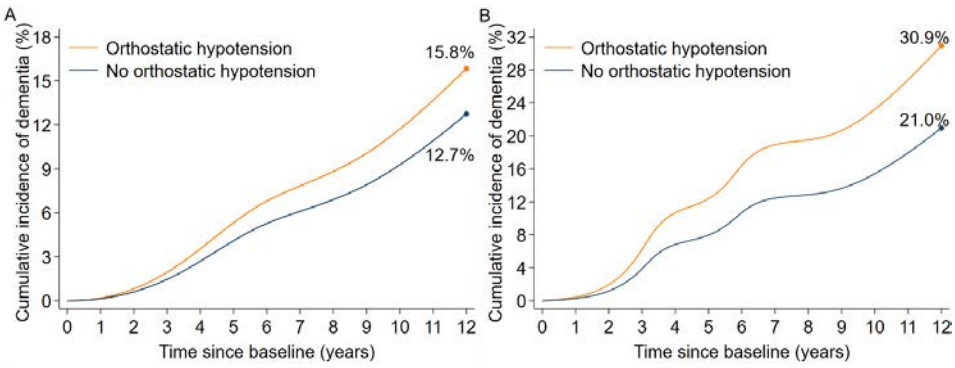

Figure 7. Standardized cumulative incidence of dementia by orthostatic hypotension status in people free of dementia (A) and in people with CIND at baseline (B) adapted from *Xia et al. 2021* (174).
Abbreviation: CIND = cognitive impairment, no dementia.

When dividing OH into asymptomatic and symptomatic OH, both asymptomatic OH and symptomatic OH were associated with higher hazards of dementia (**Figure 8**) (174). When OH was divided into non-neurogenic and neurogenic OH, both non-neurogenic OH (HR = 1.51, 95% CI = 1.08-2.11) and neurogenic OH (HR= 1.35, 95% CI = 1.02-1.79) were associated with higher hazards of dementia (174).

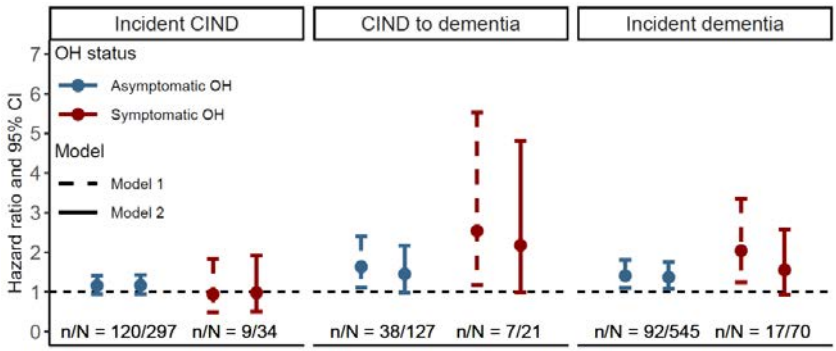

Figure 8. The associations of OH with CIND and dementia adapted from *Xia et al. 2021* (174).
Abbreviations: CIND = cognitive impairment, no dementia; OH = orthostatic hypotension.

4.4 Associations between OH and CVD and dementia (*Study III*)

In the baseline CVD-free cohort, 434 (21.9%) people had OH. Individuals with OH at baseline had a higher hazard of developing CVD (HR = 1.33, 95% CI = 1.12–1.59) and, although not statistically significant, a higher hazard of developing dementia (HR = 1.52, 95% CI = 0.97–2.38) after developing CVDs (175). These associations did not differ significantly when comparing non-neurogenic versus neurogenic OH (175). People with OH did not have a significantly higher hazard of developing dementia without having developed CVD (HR = 1.22, 95% CI = 0.83–1.81) (175).

When heart diseases and stroke/TIA were analyzed separately, individuals with OH at baseline had higher hazards of developing heart diseases (HR = 1.32, 95% CI = 1.07–1.63) and stroke/TIA (HR = 1.35, 95% CI = 0.97–1.89) (175). In addition, in people who developed heart diseases after the study baseline, those with OH had higher hazards of developing stroke/TIA (HR = 1.67, 95% CI = 1.02–2.73) and dementia (HR = 1.77, 95% CI = 0.95–3.30) (175).

In the baseline CVD cohort, 180 (25.1%) people had OH. Individuals who had OH had a higher hazard of developing dementia (HR = 1.54, 95% CI = 1.06–2.23) (175). However, the association was only observed in people who had heart diseases at baseline (HR = 1.58, 95% CI = 1.04–2.39) (175).

4.5 Associations of OH and frailty with dementia and death (*Study IV*)

At baseline, there were 825 robust people without OH, 969 frail people without OH, 233 robust people with OH, and 328 frail people with OH. Frail people without OH were similar to frail people with OH; they were older, more likely to be underweight, more likely to smoke, and more likely to have heart diseases than OH-free and robust people. Robust people who had OH were older and less likely to be overweight but otherwise similar to robust people without OH.

Compared with OH-free and robust persons, those with either frailty or OH had a higher hazard of incident dementia (**Table 6**). Frail people, regardless of OH status, had a higher hazard of death without dementia than robust people without OH, whereas people with only OH did not have a higher hazard of death without dementia (**Table 6**). In people who developed dementia during the follow-up period, frailty alone, OH alone, and OH combined with frailty were not significantly associated with the mortality rate (**Table 6**). Frailty seemed to modify the associations of OH with incident dementia, and the OH-dementia association was more evident in robust people (HR = 2.28, 95% CI = 1.47–3.54) than in frail people (HR = 1.38, 95% CI = 0.97–1.78) (P-value for the interaction term = 0.085).

Table 6. The associations of OH and frailty with transitions from no dementia to dementia and death

Transition	OH and frail status	HR (95% CI)
No dementia → dementia	OH-free and robust	1.0 (reference)
	OH-free and frail	1.98 (1.40-2.82)
	With OH and robust	2.28 (1.47-3.54)
	With OH and frail	2.73 (1.82-4.10)
No dementia → death	OH-free and robust	1.0 (reference)
	OH-free and frail	1.28 (1.05-1.54)
	With OH and robust	1.13 (0.84-1.52)
	With OH and frail	1.56 (1.25-1.96)
Dementia → death	OH-free and robust	1.0 (reference)
	OH-free and frail	1.30 (0.85-2.00)
	With OH and robust	1.49 (0.84-2.63)
	With OH and frail	1.14 (0.71-1.85)

Results are hazard ratios from multistate flexible parametric survival models adjusted for age, sex, education, smoking status, body mass index categories, hypertension, diabetes, atrial fibrillation, ischemic heart disease, heart failure, and cerebrovascular disease. Abbreviations: HR = hazard ratio, OH = orthostatic hypotension.

The standardized cumulative incidences of dementia were higher in people with either OH or frailty than robust people without OH (**Figure 9**). The differences seemed to be more evident in females (**Figure 9D-Figure 9F**) than in males (**Figure 9A-Figure 9C**). Similarly, the transition probabilities of dementia at age 65 years (**Figure 10A**) and 85 years (**Figure 10B)** were higher in individuals with either OH or frailty than in people without OH and frailty, and the differences seemed to span more extended periods in females than in males.

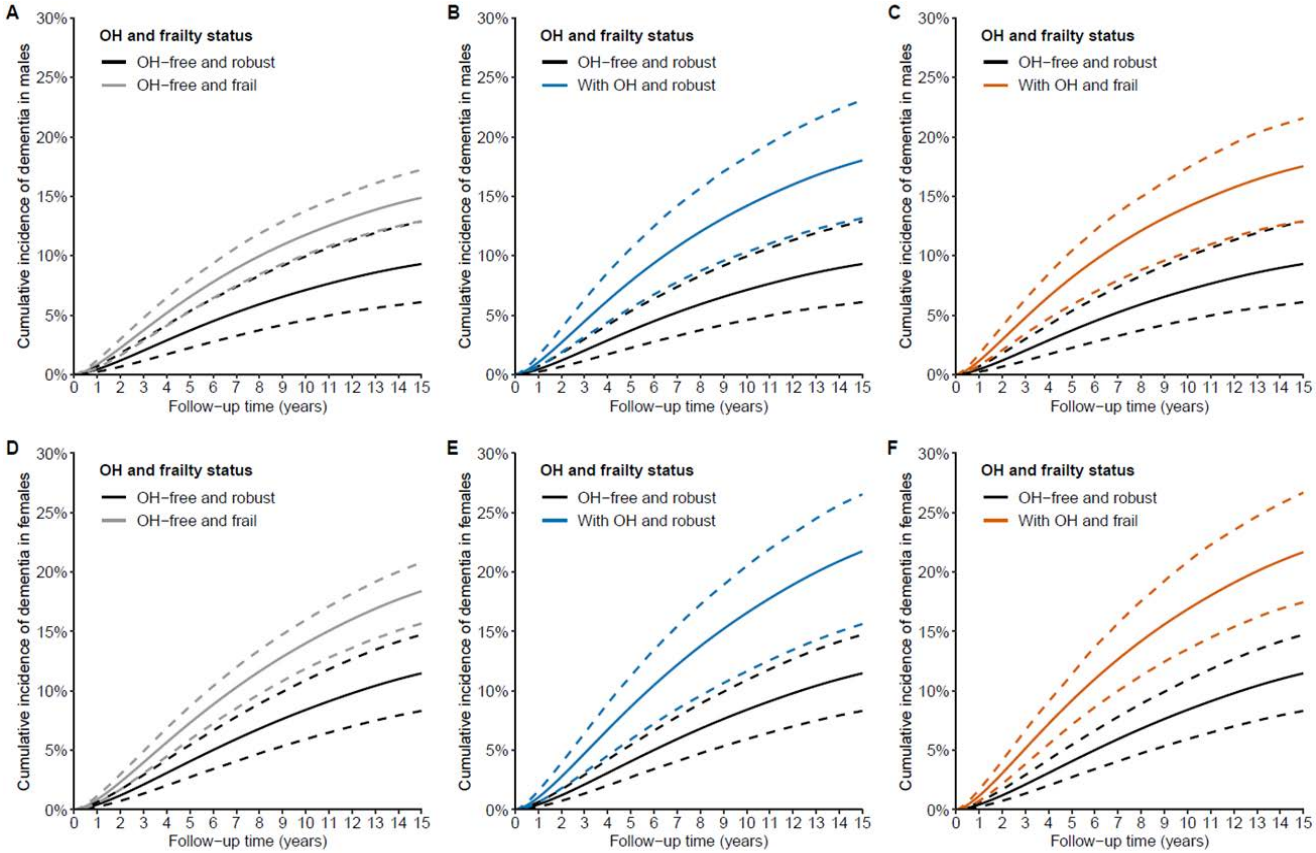

Figure 9. Standardized cumulative incidence of dementia by orthostatic hypotension and frailty status

A–C, Standardized cumulative incidence of dementia in males; D–F, Standardized cumulative incidence of dementia in females. Dashed lines are 95% confidence intervals. Abbreviation: OH = orthostatic hypotension.

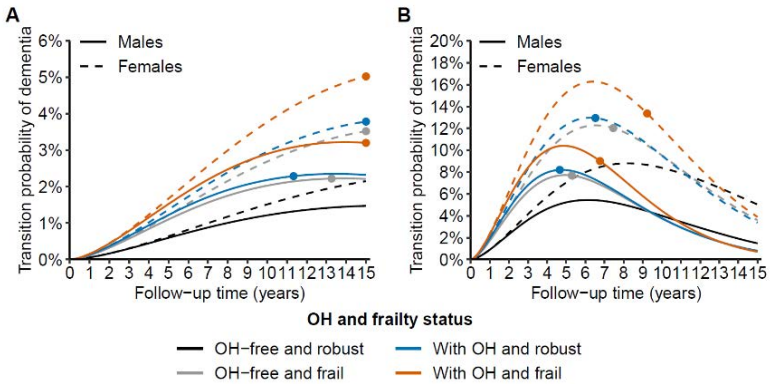

Figure 10. Transition probability of dementia in males and females by OH and frailty status for people aged 65 years (A) and for people aged 85 years (B).
Solid circles indicate when the differences in transition probabilities compared with robust people without OH become insignificant. Abbreviation: OH = orthostatic hypotension.

5 Discussion

5.1 Main findings

The doctoral thesis investigated the role of CVH levels defined by LS7 and OH in cognitive aging. The main findings of this thesis are summarized below.

(i) LS7-defined better CVH was associated with a lower risk of CIND and dementia. The associations were only observed in younger old (<78 years) but not in older old (≥78 years) adults. Younger old adults with better CVH had longer overall survival times and survival times free of CIND and dementia.

(ii) OH was related to an elevated risk of incident dementia in older adults who were initially dementia-free. OH was not associated with incident CIND but was associated with an elevated risk of developing dementia in people who had CIND.

(iii) In older adults who were originally free of CVD, individuals with OH were at a higher risk of developing CVD. In older adults who already had CVD, those with OH were at a higher risk of developing dementia than those without OH.

(iv) OH, either alone or combined with frailty, was associated with a higher risk of dementia in older adults compared with robust persons without OH. In contrast, OH was associated with a higher risk of death without dementia only in frail people.

5.2 Interpretations of the main findings

5.2.1 Life's Simple 7 and cognitive aging

The findings of *Study I* are partly in line with our recent meta-analysis, which has shown that a higher LS7 score is associated with a decreased risk of dementia in people aged ≥65 years (71). These findings support the view that good CVH is essential for maintaining cognitive health and protecting against cognitive dysfunction (92-97). *Study I* also adds new knowledge to the current literature: (i) better CVH, defined by LS7, is associated with a decreased risk of CIND and dementia in older adults under 78 years, and (ii) LS7 seems not to impact cognitive states in individuals aged 78 years and above.

Despite the important role of CVH in dementia development, the exact mechanisms through which poor CVH contributes to dementia development are not fully understood. One pathway that is supported by relatively strong evidence is vascular brain injury, including infarcts, hemorrhages, and white matter lesions, which can lead to secondary neurodegeneration or network dysfunction and cognitive impairment (92-97). A study in young adults (aged 18-30 years) showed that people with ideal CVH had greater brain volume but not abnormal white matter volume in middle age, suggesting that maintaining ideal CVH is important for promoting brain health in early life, even not through preventing white matter lesions (200). There is also emerging evidence suggesting that poor CVH may increase the burden of neurodegenerative pathologies,

which then increases dementia risk (95, 201-205). Previous studies have demonstrated associations of CVFs in middle age and old age with β-amyloid and tau deposition (95, 201-205). Furthermore, CVFs and AD pathologies might act synergistically to increase tau deposition, which can then result in cognitive decline (206-208).

On the other hand, *Study I* suggests that LS7-defined CVH may not impact cognitive states in the oldest old, which can be attributed to multiple reasons. First, LS7 aims for primordial prevention of CVD, making it less suitable for the oldest old, given the high prevalence of CVFs and CVDs in this age group (72, 209). Second, the meaning of the levels of the biological factors (i.e., BP, BMI, total cholesterol, plasma glucose) in LS7 changes with age, and ideal levels of these factors defined by LS7 become more complex in very old age. For instance, older adults can have stable and ideal BMI levels according to LS7's criteria but have decreased muscle mass and increased visceral adiposity, which may increase the risk of CVD (210). In addition, previous studies have shown that BP, BMI, and total cholesterol levels tend to decline sharply before the onset of dementia, suggesting that, in these cases, lower levels of such factors may reflect ongoing pathophysiological processes instead of better CVH (78-80). Third, current literature suggests that while many risk factors are less strongly associated with dementia risk in more advanced age, age still has a strong impact on dementia risk (211, 212). It is possible that most dementia risk in the oldest old can be attributed to the aging process, making conventional CVFs less influential. Notably, physical activity, increased consumption of vegetables and fruit, and lower sugar consumption still seem to be relevant in preventing cognitive impairment in the oldest old (212, 213). Therefore, physical activity and a healthy diet remain suitable targets for dementia prevention in the oldest old.

In summary, *Study I* suggests that LS7 can be a valuable tool to promote healthy cognitive aging in younger old adults but is not sophisticated enough to promote healthy cognitive aging in older old adults on a population level.

5.2.2 Orthostatic hypotension and cognitive aging

Although there has been increasing research on OH as a potential risk factor for dementia in recent years, it remains unclear whether OH impacts dementia development or reflects underlying subclinical or clinical conditions, such as neurodegenerative diseases, vascular aging, and frailty (106-113, 123, 135, 153). *Studies II-IV* add new insights into the relationship between OH and dementia: (i) OH is associated with an elevated risk of dementia in older adults who are initially dementia-free and CIND progression to dementia in people with CIND, (ii) OH is associated with a higher risk of CVDs in people previously free of CVD and dementia and higher dementia risk in people with CVDs, and (iii) OH, whether accompanied by frailty or not, is associated with elevated dementia risk. The findings in *Studies II-IV* held even after accounting for age, vascular risk factors (e.g., hypertension, diabetes), prevalent CVDs (e.g., heart failure), medication use (e.g., antidepressants), and neurogenic OH status.

The findings of *Study II* are consistent with previous population-based studies, which have demonstrated that older adults who have OH are at a higher risk of dementia (107, 108, 113). Population-based cohort studies in middle-aged adults, who are less likely to be affected by age-related neurodegenerative diseases, also suggest that individuals with OH have an elevated risk of dementia (109, 110). The associations between OH and dementia subtypes reported in previous studies were inconsistent, with one study involving middle-aged adults suggesting a stronger association between OH and vascular dementia than AD and two studies in older adults suggesting no significant differences in the associations of OH with AD and vascular dementia (107-109). In *Study II*, OH was related to an increased risk of AD, but there were not enough vascular dementia cases to investigate the association between OH and vascular dementia. It is also worth mentioning that dementia in older adults is more likely to be attributed to mixed brain pathologies than a single pathology (17). Therefore, future research with fluid biomarkers, neuroimaging biomarkers, and pathologic evaluations for brain pathologies is needed to clarify the relationships between OH and dementia subtypes and to understand the underlying mechanisms. *Study II* also lends support that OH may accelerate the progression from CIND to dementia, which was previously demonstrated in a memory clinic-based study (112). Another novel finding in *Study II* is that both asymptomatic OH and symptomatic OH were associated with an elevated risk of dementia. Given that most older adults with OH do not experience symptoms, whether it is beneficial to actively evaluate OH status in older adults remains an important question.

Study III, on the other hand, provides evidence that the intermediate development of CVDs may partly account for the OH-dementia association. Previous studies have evaluated the associations between OH and CVDs or dementia separately and generally support OH being associated with an elevated risk of CVDs and dementia (103-105, 114). However, no studies have evaluated the associations between OH and CVDs and dementia together and taken the temporal order of CVDs and dementia into account. *Study III* found that OH was associated with a higher risk of CVDs in people without CVDs who had not developed dementia. The associations of OH with heart diseases and TIA were comparable. In addition, the association between OH and dementia in people who have not developed CVDs was weak. Another novel finding of *Study III* is that OH was related to an increased risk of dementia in people who had heart diseases. These findings reveal a potential event history trajectory, spanning from the absence of CVDs to its onset and subsequent onset of dementia, that OH may influence. However, this study could not fully exclude the influence of confounding factors, particularly vascular aging (95, 123). Therefore, further research with measures of vascular aging is warranted to verify the findings in *Study III*.

The findings of *Study IV* provide further evidence that OH may be a potential risk factor for dementia. Previous research has shown that OH and frailty, which has been considered a marker of biological aging, often co-occur in older adults (149, 150, 153). In addition, both OH and frailty have been associated with elevated dementia risk (106-113, 154-167). Nevertheless, previous studies relating OH to dementia risk have not taken

frailty into account. *Study IV* demonstrated that OH was related to a higher risk of dementia in both robust and frail people, and the OH-dementia association was more evident in robust people than in frail people. In contrast, OH was associated with a higher rate of death without dementia in frail people but not in robust people. These findings suggest that OH may confer an increased risk of dementia regardless of frailty status.

The mechanisms through which OH may impact the development of CVDs and dementia remain to be understood. It is hypothesized that reduced end-organ perfusion and subsequent ischemic injury are key mechanisms explaining the effects of OH on adverse health outcomes (118, 120, 132-135, 142, 148). Earlier research has shown that people with OH have a decreased subendocardial viability ratio (indicating the myocardial oxygen supply is possibly insufficient in comparison to the demand for oxygen) and higher levels of Hs-troponin T and NT-proBNP (markers of myocardial injury and cardiac stress) (120, 142, 148). OH may also induce hypoperfusion in the brain and cause cerebral ischemic injury, which then contributes to cognitive dysfunction (132-134). Previous studies have shown that people with OH have more severe white matter hyperintensity burdens and are more likely to have lacunes, which can result from cerebral hypoperfusion and subsequent cerebral ischemic injury (136, 137, 140, 141). Interestingly, a study based on SNAC-K found an association between OH and enlarged global and lobar perivascular spaces, which was evident only in *APOE* ε4 carriers after taking white matter hyperintensity burden into account (138). It was hypothesized in this study that OH and *APOE* ε4 might act synergistically to increase amyloid deposition (138). Nevertheless, most of the evidence is from cross-sectional studies in which biomarkers were measured at the same study visit as OH; thus, it is impossible to establish temporality and causality based on the current evidence. Longitudinal studies are needed to verify these findings and elaborate on the mechanisms that can account for the associations of OH with CVDs and dementia.

In summary, *Studies II-IV* found that OH was related to an elevated risk of CVDs and dementia in older adults, even after accounting for age, CVFs, comorbidities, and frailty. These study findings, together with previous research, suggest that it is possible that OH is a potential risk factor for dementia.

5.3 Methodological considerations

This doctoral thesis investigated the roles of CVH and OH in cognitive aging in older adults through an epidemiological approach. The four studies in this thesis were population-based cohort studies using secondary data from the SNAC-K. The main strengths of the studies include a long follow-up period, comprehensive measurements of exposures, outcomes, and covariates, and standardized measurements conducted by trained staff following study protocols. However, there are also limitations in the studies. Limitations of the thesis from methodological aspects that are essential for epidemiological studies are discussed below.

5.3.1 Selection bias

Selection bias refers to the bias when estimates from the study population, either disease occurrence or associational estimates, are not valid estimates for the source population, where the study population was from. Selection bias can be divided into two types: one due to collider bias (i.e., conditioning on the common factor influenced by both exposure and outcome) and another due to conditioning on effect modifier (214).

Selection bias usually arises during the selection of participants and over the follow-up period when participants can withdraw from the studies. This thesis used data from the SNAC-K, which adopted a random sampling strategy to select participants who are representative of older adults living in Kungsholmen, a central area of Stockholm. Among the 5111 individuals randomly selected, 321 were ineligible (e.g., deaf, could not speak Swedish), and 200 were deceased. Of the 4590 eligible and alive individuals, 3363 individuals agreed to participate in the SNAC-K. The individuals who declined to participate had a higher mortality rate within two years following baseline than those who participated (215). Therefore, it is reasonable to postulate that people who participated in the SNAC-K were healthier than the population of adults aged ≥60 years living in Kungsholmen. Some participants withdrew between baseline and the first follow-up SNAC-K study visit. People who withdrew from the study were younger, had lower educational levels, had worse CVH, and were more likely to have CIND (172). However, the withdrawal was not associated with OH status or OH severity (175). Nevertheless, the final analytical samples in the thesis were healthier than the source population, which typically leads to an underestimation of the effects of risk factors in the field of dementia research (216).

5.3.2 Measurement error

5.3.2.1 Measurement errors in study exposures

The measurements of the exposures and outcomes in this thesis are subject to measurement errors. LS7 investigated in *Study I* included seven modifiable CVFs, three self-reported (i.e., smoking, physical activity, and healthy diet), and four measured objectively (i.e., BMI, BP, fasting plasma glucose, and total cholesterol). As there were no detailed data to define physical activity according to the AHA criteria and no fasting plasma glucose data, we applied a modified version of the AHA criteria, which led to measurement errors. However, this source of measurement errors is due to the study design and is not dependent on the study outcome or covariates. Another source of measurement errors in LS7 factors in *Study I* is that self-reported factors, especially physical activity and diet, are prone to underreporting and overreporting (217, 218). The four objectively measured LS7 are less prone to measurement errors except for BP measurements, which can be affected by various factors (219-221). White coat hypertension may be a particular problem, which tends to result in overestimating BP levels (221). As the LS7 factors were measured before the occurrence of the study outcomes, measurement errors in those factors are likely to be independent of the

study outcomes but may dilute the associations of LS7 with the cognitive states in *Study I* (222).

OH, the exposure in *Studies II–IV*, is also subject to measurement errors. OH status can fluctuate during the day and, similar to measurements of sitting BP, can be affected by incorrect handling during the measurement. In the SNAC-K, OH is measured by trained physicians using the auscultatory method, which reduces the risk of measurement errors. The time of the day when OH is evaluated is not dependent on the cognitive status and other medical conditions of participants. Therefore, the misclassification of OH resulting from measurement errors is likely to be non-differential, which may underestimate the relation of OH with the study outcomes (222).

5.3.2.2 Measurement errors in study outcomes

The clinical diagnosis of dementia is robust as it was performed and confirmed by trained physicians and neurologists using validated instruments following standard criteria. Diagnosing dementia at each study visit in population-based studies has advantages over identifying dementia cases in the Swedish registers, as a previous study showed that the Swedish NPR and CDR tended to underdiagnose dementia and had significantly delayed diagnoses of dementia (223). For people who died between study visits, a neurologist ascertained dementia status by reviewing these people's medical charts, and we tried to determine if those individuals had dementia through records in the NPR and CDR (172, 174, 175). These approaches optimized the usage of available data and reduced the risk of misclassifying people with dementia as not having dementia.

CIND in *Studies I–II* was defined using a neuropsychological battery that comprehensively tested major cognitive domains relevant to dementia (177). However, there is no consensus on what cognitive tests must be included to define CIND and how to define cognitive impairment based on the cognitive tests in research settings. Previous meta-analyses showed varying conversion rates of MCI, and a recent study showed that multiple definitions of cognitive impairment all poorly predicted future dementia risk (34, 224). These findings raised questions regarding the robustness of the definition and diagnostic tools of CIND in research settings. It is likely that CIND misclassifications exist in *Studies I and II*. The influence of this misclassification is difficult to speculate before the construct and the diagnosis of CIND are further refined.

Study III investigated CVDs as study outcomes, and CVDs were ascertained in the records in the Swedish NPR and by the SNAC-K physicians. The validity of diagnoses of the CVDs in the NPR is high, with sensitivities and positive predictive values >90% (183-188). Some participants without histories of CVDs had abnormal electrocardiograms indicative of ischemic heart disease and atrial fibrillation during the physician interviews. In these cases, electrocardiogram findings were recorded, and the participants were advised to consult their general physicians. In rare cases, the participants had to be sent to emergency care. A combination of diagnostic records in the NPR and ascertainment

by physicians improved the sensitivity and specificity of diagnosing CVDs and reduced the risk of misclassification of CVDs in *Study III*.

5.3.2.3 Measurement errors in study covariates

The statistical models in *Studies I–IV* adjusted for covariates to control for confounding bias. However, the covariates are also prone to measurement errors. For instance, smoking status was measured by answering simple questions such as "Are you, or have you ever been a smoker?". This type of measurement lacks granularity in evaluating smoking habits and can lead to measurement errors of the health risk burdens (e.g., atherosclerosis) that smoking habits may carry. The measurement errors in the covariates generally lead to insufficient control of confounding bias, usually referred to as residual confounding (225).

5.3.3 Confounding bias

Confounding bias refers to the bias caused by factors that impact both exposures and outcomes, which lead to statistical associations between the exposures and outcomes, even if there is no direct relation between the study exposure and the outcome. Confounding bias is a ubiquitous bias that affects the validity of epidemiological studies. There are different ways of addressing confounding bias due to measured confounders at the stage of statistical analysis, including but not limited to covariate adjustments, propensity score matching, and inverse probability weighting methods. This thesis used the covariate adjustment method to control confounding bias due to measured confounders, as it is straightforward and has shown good performance in epidemiological studies (226).

Unmeasured confounders are more difficult to address, but methodologies have been continuously studied to address confounding due to unmeasured confounders. At the study design phase, alternative study designs that may control for unmeasured confounding include but are not limited to sibling studies and self-controlled case series (227, 228). At the statistical analysis phase, unmeasured confounding can be controlled through instrument variable methods and sensitivity analyses (228).

For each individual study in the thesis, we chose and adjusted for factors that could confound the associations between the study exposure and outcome based on literature reviews. However, there were imperfectly measured confounders (e.g., education level and smoking status) and unmeasured confounders (e.g., neurodegeneration and vascular aging). The issue of unmeasured confounders is more concerning in the studies on the associations between OH and cognitive outcomes, as OH can be caused by various conditions, including neurodegenerative diseases and vascular aging (118, 119, 123). Reverse causation, where the study outcome causes the study exposure instead of the study exposure affecting the study outcome, is one type of confounding bias. In the studies of OH in relation to cognitive outcomes, we did not have data on the underlying brain pathologies. However, in *Study II*, we introduced a three-year lag period between OH exposure and dementia development, and the

association between OH and dementia remained. In addition, when OH was divided into non-neurogenic and neurogenic OH, both were related to an increased risk of dementia. Furthermore, previous studies found that, even in people with Parkinson's disease and people with multiple system atrophy, OH was also related to an elevated risk of dementia, and the association seemed not to be entirely due to shared neuropathological burdens (e.g., α-synucleinopathies, β-amyloid plaques) (229, 230). Therefore, more research must be done to understand the mechanisms underlying the association between OH and dementia before attributing this association entirely to reverse causation.

5.3.4 Generalizability

Generalizability refers to the ability of the estimates from the study population to be generalized to a different population (i.e., target population) that can either include the study population, overlap with the study population, or have no overlap with the study population. In some contexts, the concept of transportability is used when the target population only partly overlaps or has no overlap with the study population (231). The generalizability of results from a population is usually affected when there are factors that can modify the effects of the exposure on the outcome, and the distributions of effect modifiers are different in the study population and the target population (214). The study population in this thesis is relatively healthier and has better socioeconomic status than other regions of Sweden. In addition, the study participants are mainly white. Given that health status, socioeconomic status, and race can imply susceptibility to the study exposures, the study results in the thesis may not be fully generalizable to populations with different distributions of health status, socioeconomic status, and race.

6 Conclusions

The findings of the four studies in the present thesis suggest that older adults with better CVH defined by LS7 before late life have decreased risk of CIND and dementia and longer life years living in normal cognition. The findings of this thesis also suggest that OH could be a potential risk factor for the development of cognitive dysfunction, including CIND and dementia. The association between OH and dementia could not be fully explained by common CVFs and frailty but may be partly accounted for by the intermediate development of CVDs. However, there are methodological limitations in the studies, particularly residual confounding. Future research adopting more advanced methods and with more comprehensive data is needed to verify these findings and understand the mechanisms that can explain the effects of CVH and OH on cognitive aging.

7 Points of perspective

7.1 Implications of the study findings

Dementia is a major barrier to healthy aging, and the burden of dementia is increasing with population aging. Identifying and managing risk factors and promoting protective factors are important to combat the increasing burden of dementia. This doctoral thesis investigated several modifiable protective and risk factors for cognitive aging, and the findings have several public health and clinical implications.

The first study supports the potential of using the available tool, LS7, to promote longer life with good cognitive health in older adults on a population level. The benefits of maintaining ideal CVH following LS7's recommendations also exist in people genetically predisposed to developing dementia. In addition, LS7 does not require complex measurements and thus may not only be a useful tool to monitor CVH but also cognitive health (232). However, promoting LS7 may only be beneficial in younger old adults (e.g., <80 years). LS7 lacks consideration of the complex health conditions that are prevalent and vary between individuals in older old adults. More sophisticated, comprehensive, and person-centered strategies are needed for dementia prevention in older old adults.

The three studies investigating the role of OH in cognitive aging provide evidence for OH being a potential modifiable risk factor for dementia. The effects of OH on falls and quality of life in older adults and in patients with neurodegenerative diseases are the major concerns regarding OH (118). The potential detrimental effects of OH on cognitive aging have been controversial. *Studies II-IV* in this thesis sought to delineate the non-causal pathways (e.g., confounding bias due to shared risk factors) from potential causal pathways that may explain the statistical associations between OH and dementia. The findings suggest it is possible that OH is a risk factor for dementia. In addition, OH may accelerate cognitive deterioration in people who already have CIND or CVDs. Therefore, it may be beneficial to manage OH in older adults to lower the risk of developing dementia, especially in older adults with CIND and CVDs, as they are already at a higher risk of dementia. The ideal prevention and management of OH is achievable through a person-centered approach that involves identifying and managing the causes of OH, patient education, and pharmaceutical treatments (118). Furthermore, OH in older adults is usually asymptomatic, meaning most older adults may not be aware of their OH status. A recent study showed that at-home self-assessed OH was reliable, acceptable, and safe for older adults (233). It is worth investigating if actively detecting and managing OH by clinicians and self-management of OH in older adults is beneficial and cost-effective.

7.2 Future directions

This thesis provides evidence in support of using LS7 to promote cognitive health and the possibility of OH being a modifiable risk factor for cognitive dysfunction in older adults. However, more research needs to be done before the study findings can be translated into practice.

Given the limitations discussed above, the study findings in this thesis need to be verified by future studies. Studies with better measurements (e.g., comprehensive evaluation of the causes of OH, neurodegenerative biomarkers, and measures of vascular aging) and with alternative study designs that are more robust to confounding bias, such as twin-based studies and studies using instrument variables, can overcome the shortcomings of the thesis and validate our study findings. Furthermore, studies with repeated measurements of biomarkers (e.g., neuroimaging biomarkers) may help in understanding the mechanisms accounting for the associations of CVH and OH with cognitive aging.

When investigating the associations of LS7 with cognitive states in younger old adults and older old adults, we used 78 years as the cut-off for age due to the design of the SNAC-K, which was arbitrary. Future studies with sufficient numbers of people in each age group may investigate at what age LS7 can impact cognitive health, which is important for finding the right target population to apply LS7 to promote healthy cognitive aging. In addition, future research can evaluate if Life's Essential 8, which refined LS7 and additionally added sleep as a CVH metric, has more impact on cognitive status in older adults (234).

Lastly, conventional CVFs have been included in prediction models for CVD and dementia (235, 236). However, OH, which can capture the excessive risk of CVD and dementia that conventional CVFs cannot account for, has not been considered in prediction models for CVD and dementia. Future research should investigate if adding OH can improve the performance of prediction models for CVD and dementia risk.

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10 Appendix

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991–2023.

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.

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

2006

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

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

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

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

2007

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

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

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

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

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

2008

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

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

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

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

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

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

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

2009

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

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

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

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

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

2010

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

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

2011

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

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

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

2012

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

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

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

2013

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

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

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

Svärd Joakim. Emotional facial processing in younger and older adults.

Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.

Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.

Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.

Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.

Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.

Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.

Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.

Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018

Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.

Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.

Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.

Sjöberg Linnea. Using a life-course approach to better understand depression in older age.

Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

2019

Seblova Dominika. Causal effects of education on cognition – How do we generate evidence?

Berggren Rasmus. Cognitive development and educational attainment across the life span.

Vetrano Davide Liborio. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.

Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.

Pan Kuan-Yu. Impact of psychosocial working conditions on health in older age.

Avelar Pereira Bárbara. Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging

Morin Lucas. Too much, too late? Drug prescribing for older people near the end of life.

de Boer Lieke. Dopamine, decision-making, and aging: Neural and behavioural correlates.

Ek Stina. Predictors and consequences of injurious falls among older adults: A holistic Approach.

Ding Mozhu. The role of atrial fibrillation in cognitive aging: a population-based study

2020

Dintica Cristina Silvia. Oral health & olfactory function: what can they tell us about cognitive ageing?

Payton Nicola Maria. Understanding preclinical dementia: early detection of dementia through cognitive and biological markers.

Li Xin. The relation among aging, dopamine-regulating genes, and neurocognition.

Grande Giulia. Development of dementia in older adults: the body-mind connection.

2021

Shang Ying. How can older adults combat diabetes to achieve a longer and healthier life?

Sif Eyjólfsdóttir Harpa. Unequal tracks? Studies on work, retirement and health.

Sundberg Louise. Better all the time? Trends in health and longevity among older adults in Sweden.

2022

Saadeh Marguerita. Enjoying life and living healthier: impact of behavioral and psychosocial factors on physical function in old age.

Naseer Mahwish. Why do older adults seek emergency care? The impact of contextual factors, care, health, and social relations.

Guo Jie. Unraveling the relationship between body mass index and cardiometabolic disease, dementia, and survival in old age.

2023

Jing Wu. Ambient air pollution and transportation noise: how they affect mental health in older adults.

Nathalie Frisendahl. Injurious falls in older adults: early identification of individuals at risk of falls—from observational studies to implementation.

Yuanjing Li. Cardiovascular health and brain aging: a population-based MRI study.