Alzheimer's disease and vascular dementia in population-based studies

Mats Ribbe

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

UNIVERSITY OF GOTHENBURG

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Mats.ribbe@neuro.gu.se

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To my loving family

ABSTRACT

Dementia, a clinical syndrome with several profiles and causes, is characterised by a decline in cognitive functions, including memory, learning, executive function, attention, language, and social ability. The most common forms of dementia are Alzheimer's disease and vascular dementia. As life expectancy is increasing worldwide and age is one of the strongest risk factors for dementia, the prevalence of dementia will likely increase. This thesis explores pathophysiological hallmarks of Alzheimer's disease and vascular events as well as risk factors associated with dementia development in older individuals.

In study I, we explored the prevalence of dementia in the oldest old and the relationship between stroke, transient ischemic attack, and dementia. We found that dementia was very common in the oldest old, and prevalence of dementia was higher in women than in men. However, in this unique group of oldest old, the association between stroke and development of dementia diminished.

In study II, we explored biological markers of Alzheimer's disease in relation to mortality. Alzheimer's disease has measurable pathological biomarkers in the cerebrospinal fluid (Aβ42 and T-tau). The levels of these pathological biomarkers in 85-year-olds was associated with survival.

In study III, we compared two cohorts of 85-year-olds born 22 years apart. We found that 85-year-olds examined between 2008 and 2010 had lower blood pressure than 85-year-olds examined 22 years earlier. In both cohorts, participants with dementia had lower blood pressure than those without dementia.

In study IV, we investigated whether high blood pressure was associated with brain atrophy in Alzheimer's specific brain regions. We found that hypertension in 70-year-olds without dementia was related to atrophy in brain regions often affected in Alzheimer's disease, and atrophy was more widespread in those with longer duration of hypertension.

In summary, this thesis presents common risk factors for dementia and further investigates hallmarks in Alzheimer's disease with the aim to contribute to better understanding of Alzheimer's disease and vascular dementia.

KEYWORDS: Alzheimer's disease, cerebrospinal fluid, dementia, hypertension, magnetic resonance imaging, older, survival, vascular dementia.

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SAMMANFATTNING PÅ SVENSKA

Demens innebär en kognitiv funktionsnedsättning som kan orsakas av många olika sjukdomar. Gemensamt är att hjärnans högre funktioner sviktar. Den vanligaste orsaken till demens är Alzheimers sjukdom, som uppskattas till minst 60% av alla demensfall. Starten för Alzheimers sjukdom anser vi är bildandet av ett protein (Aβ42), som för med sig en kaskad av händelser, som så småningom orsakar Alzheimers sjukdom. Den näst vanligaste orsaken till demens är vaskulär demens, det vill säga att blodförsörjningen till hjärnan försämras. Vaskulär demens kan uppträda till exempel efter en stroke, som skadat hjärnan så att kognitiva nedsättningar uppstår.

Hos de äldsta med demenssjukdom är det vanligt att man finner ett blandtillstånd, det vill säga att både Alzheimers patologiska förändringar (såsom fynd av Aβ42 protein i hjärnan) och skador i hjärnan till följd av påverkad blodförsörjning upptäcks samtidigt.

Målet med denna avhandling har varit att både undersöka riskfaktorer för demenssjukdom, så som högt blodtryck och stroke och med hjälp av magnetkameraundersökning och ryggvätskeprov fortsätta kartlägga Alzheimers sjukdom.

Uppskattningar visar att det idag finns cirka 50 miljoner människor världen över, som lider av någon typ av demenssjukdom. Om bara 20 år beräknas denna siffra ha dubblerats till 100 miljoner människor. Den största ökningen förväntas ske i låg- och medelinkomstländer, där möjligheten till god vård och omsorg många gånger är begränsad. Detta visar på vikten av att fortsätta kartlägga orsakerna till demens för att på så sätt kunna, om möjligt, förebygga och förhindra demensutveckling.

Hög ålder är en viktig riskfaktor för utvecklandet av både Alzheimers sjukdom och vaskulär demens. Dessa sjukdomar förekommer även hos yngre, men är ovanliga. Den stora majoriteten, som utvecklar Alzheimers sjukdom och vaskulär demens, är äldre. Ändå är äldre ofta en eftersatt och sällan undersökt grupp när det kommer till forskning. Därför vill jag med min forskning undersöka just äldre.

LIST OF PAPERS

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

I. **A Population-Based Study on Dementia and Stroke in 97 year olds.**

Andersson* M., Guo X., Börjesson-Hanson A., Liebetrau M., Östling S. and Skoog I.
Age & Ageing. 2012 Jul;41(4):529-33.

II. **Amyloid ß42 and Total Tau Levels in Cerebrospinal Fluid Associate with Survival in an 85-year-old Population-Based Cohort Followed Until Death.**

Ribbe M., Kern S., Börjesson-Hanson A., Östling S., Zetterberg H., Blennow K. and Skoog I.
Dementia Geriatric Cognitiv Disorder 2019;47(1-2):114-124.

III. **Time Trends in the Relation Between Blood Pressure and Dementia in 85-year-olds.**

Ribbe M., Kern S., Wetterberg H., Rydén L., Zettergren A., Guo X. and Skoog I.
Submitted.

IV. **The Effect of High Blood Pressure on Alzheimer's Specific Brain Regions.**

Ribbe M., Kern S., Machado A., Lindberg O., Westman E., Zetterberg H., Blennow K., Zettergren A. and Skoog I.
Submitted.

**Today, Ribbe*

CONTENT

ABBREVIATIONS

AD	Alzheimer's Disease
ADL	Activities of Daily Living
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
CAA	Cerebral Amyloid Angiopathy
CVD	Cardiovascular Disease
CSF	Cerebrospinal Fluid
DBP	Diastolic Blood Pressure
DSM	Diagnostic and Statistical Manual of Mental Disorders
EWHPE	European Working party High blood Pressure in Elderly
HDL	High-Density Lipoprotein
HYVET	Hypertension in the Very Elderly Trial
ICD	International Statistical Classification of Diseases
ICV	Intracranial volume
LDL	Low-Density Lipoprotein
MCI	Mild Cognitive Impairment
MID	Multi-Infarct Dementia
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NFTs	Neurofibrillary Tangles
PET	Positron Emission Tomography
PHFs	Paired Helical Filaments
SHEP	Systolic Hypertension in the Elderly Program
SBP	Systolic Blood Pressure
TIA	Transient Ischemic Attack
VaD	Vascular Dementia
VADAS	Vascular Dementia Assessment Scale
VCI	Vascular Cognitive Impairment
WML	White-Matter Lesions
WHO	World Health Organization

BRIEF DEFINITIONS

Dementia	Umbrella term with symptoms of disturbed function in higher cortical brain regions.
Alzheimer's disease	A progressive brain disorder with impaired memory and thinking skills.
Vascular dementia	Dementia caused by interruptions in the supply of blood to the brain.
Stroke	Both haemorrhagic and ischemia of cerebral blood vessels with clinical symptom duration $\geq$24 hours.
Transient ischemic attack	Focal neurological deficit of a stroke but with restitution within 24 hours.
Amyloid beta 1-42 (Aβ42)	A 42-amino-acid sequence peptide derived from amyloid precursor protein (APP). Biomarker for Alzheimer's disease.
Total amount of Tau (T-tau)	Protein that mainly stabilizes microtubules in neuron axons. Biomarker for general neurodegeneration.
Phosphorylated Tau (P-tau)	Phosphorylated Tau forms neurofibrillary tangles. Biomarker for Alzheimer's disease.
Epidemiology	Branch in medicine that studies population distributions and determinants of health-related conditions and events.
Birth cohort	A population born during the same time period (e.g., 85-year-old born in 1923).
Cohort effect	Every cohort is exposed to different health-related factors (e.g., advancement in medical treatments and World War II).

1 INTRODUCTION

This introduction presents a brief introduction of dementia and subtypes of dementia.

1.1 DEMENTIA

Dementia is not a specific disease but an umbrella term for different subtypes of dementia. All patients with dementia diseases display symptoms that originate from some insult to the brain, ultimately causing cognitive impairment that advances over time. Dementia negatively affects a person's thinking, behaviours, and abilities to perform specific tasks, symptoms that compromise higher cortical functions. According to the Diagnostic and Statistical Manual of Mental Disorders III-R (DSM) (used for diagnoses of dementia in study I-IV), the primary diagnosis criterion for dementia is decline in both memory and thinking.

1.1.1 HISTORICAL BACKGROUND

The term "dementia" is derived from the Latin word *demens* – 'without mind'. The Greek physician Hippocrates of Kos (c. 460-c.370 B.C.), also known as the "Father of Medicine" and who was aware of the mental decline associated with old age, described dementia as an unavoidable consequence of aging and therefore did not consider it an abnormality [1, 2].

1.1.2 CAUSES OF DEMENTIA

The most common types of dementia are Alzheimer's disease (AD) and vascular dementia (VaD) [3]. Dementia diagnostics should assess the patient's global as well as daily life functioning as there needs to be clear evidence of decline from a previous level. Different regions of

the brain may be affected to different degrees in different types of dementia. For example, AD patients present with early loss of memory and linguistic function, whereas VaD patients often present with loss of executive functions before memory impairment [4-6].

There is no easy way to identify early stages of dementia as many conditions and diseases affect cognitive functions that are not due to dementia. Therefore, a patient presenting cognitive decline needs to be evaluated for many possible causes. Although uncommon, it is important to consider secondary dementia, including metabolic causes (e.g., alcohol, B12-defiency, and hypothyreosis), cerebral causes (e.g., hydrocephalus, chronic subdural hematoma, and other intracranial processes including tumours), and infections (e.g., blood borne infections, encephalitis, and prion diseases) as some conditions are treatable.

1.1.3 CORRELATION BETWEEN AGE AND DEMENTIA

With increasing age, dementia is more common [7-10] (although dementia is not a normal part of ageing (see 1.1.7. Normal aging or disease?). Some cognitive functions deteriorate with age (e.g., intellectual speed and episodic memory), but most cognitive functions are preserved. Nevertheless, the high correlation of dementia with increasing age needs to be addressed.

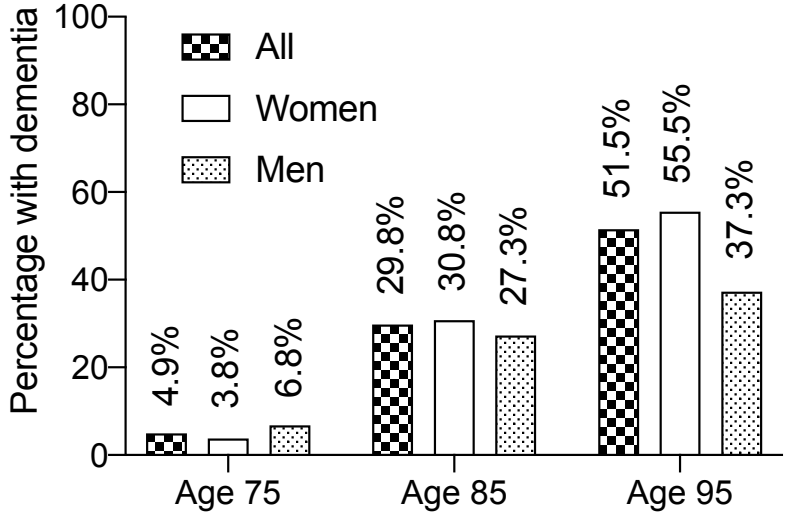

Figure 1. Prevalence of dementia in different ages

The following studies included participants born in 1901–02, presented with dementia at 75-, 85-, and 95-years of age:
[a] Secular trends in the prevalence of dementia and depression in Swedish septuagenarians 1976–2006 (Wiberg P, 2013) [7].
[c] A population-based study of dementia in 85-year-olds (Skoog I, 1993) [8].
[d] The prevalence of dementia in 95-year-olds (Börjesson-Hanson A, 2004) [9].

1.1.4 SEX DIFFERENCES IN DEMENTIA

In absolute numbers, more women than men have dementia [4, 11], especially after the age of 85 [12, 13]. This difference is perceived mainly because of differences in life expectancy. That is, because women live longer on average [12]. However, data derived from a population-based study on the oldest old show that few men survive to be the oldest of the old, but among surviving men dementia is less common (Figure 1) [9]. Although men surviving to extreme ages is

less common than women, these men may have less risk factors related to dementia [14], an issue that will be discussed further. Women surviving to a higher age probably does not completely explain this difference in dementia prevalence in women and men. Besides biological differences (e.g., hormones and differences in blood pressure (BP) levels [15]) there have also been historical inequality, with disadvantage in education and socio-economic situations for women [16].

1.1.5 NUMBER OF PEOPLE WITH DEMENTIA WORLDWIDE

Presently, approximately 50 million people worldwide are affected by dementia [17] and the number of people who will develop dementia probably will increase significantly [18, 19] (Figure 2). This increase in dementia cases will mainly be because the number of older individuals worldwide will increase with advances in health care and preventive care (especially in low and middle-income countries). That is, ageing is the greatest risk factor for development of dementia. However, recent population-based studies suggest that age-specific risk of dementia may be declining [18]. This decline, at least in high-income countries, could be due to lifestyle changes and better prevention of cardiovascular risk factors [17, 18].

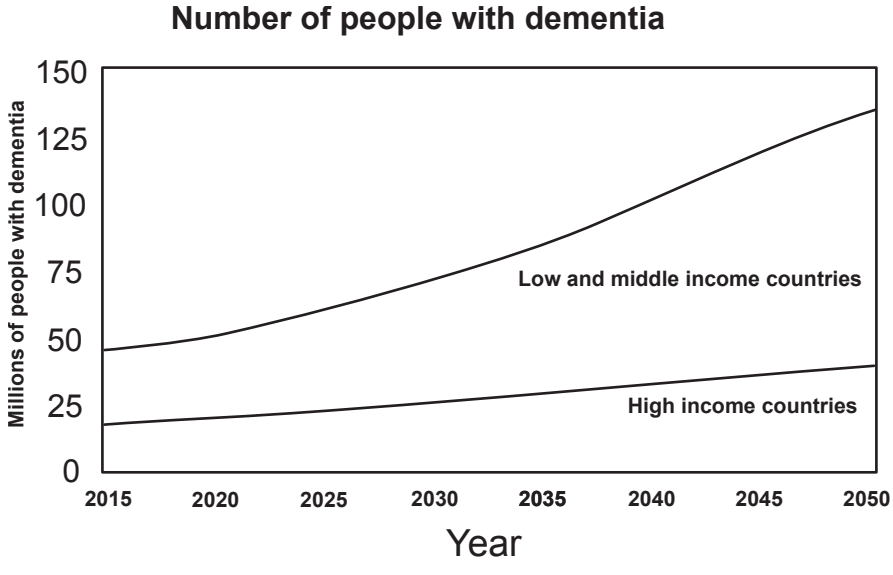

Figure 2. Number of people with dementia

Worldwide prevalence of dementia in 2015 estimation is 44.3 million people and 135.5 million in 2050 [17]. Note the increase especially in low- and middle-income countries, which is probably due to increases in life expectancy, but also an increase in risk factors (e.g., high BP, high BMI, and diabetes) [17]. Forecast in developing countries are a 100% increase between 2001 and 2040, and a 300% increase in India, China, and south Asian countries [19].

Figure acquired and modified from World Alzheimer Report, 2015.

1.1.6 COHORT EFFECT

We need to consider that studies based on samples from the general population, include people living in different time eras [20] as events during their lives are likely to affect both risk factors for dementia and survival. For example, new medications (e.g., antihypertensive drugs and cholesterol treatments) as well as historical events (e.g., widespread poverty, World War II and the Great Depression) significantly affected people's lives and ultimately population-wide risk factors [20] (Figure 3).

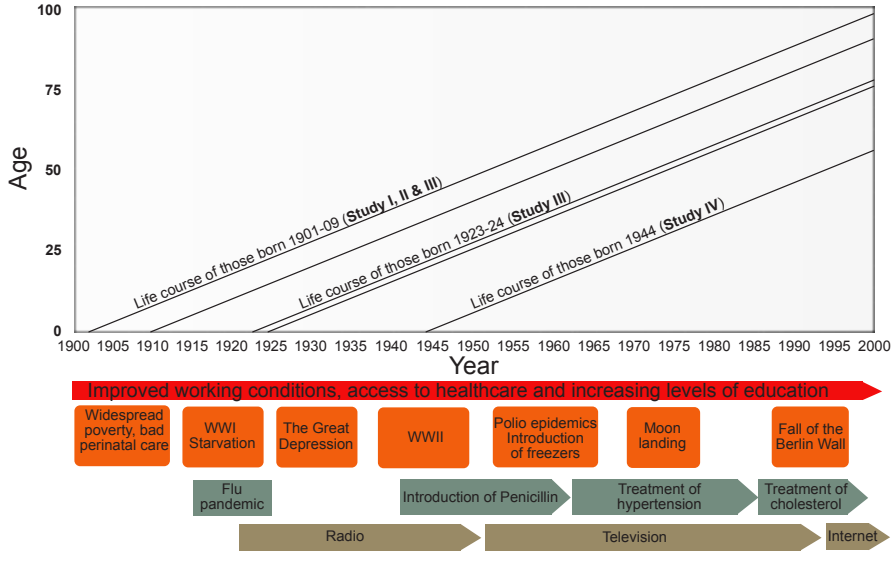

Figure 3. Life courses of people from different time eras

We need to consider at what age and during what time era the individual lived when evaluating risk factors for dementia

Figure acquired and modified from author Skoog I. (2016) [20].

1.1.7 NORMAL AGING OR DISEASE?

Within normal aging there is a range from, what many would consider successful aging to unsuccessful aging. According to the "threshold hypothesis", aging results in degeneration of, for example, nerve cells, and at a certain level this nerve cell degeneration reaches a critical threshold, which results in clinical manifestations. People who fall within the "successful aging" range may possess a high reserve before reaching this threshold [21]. In addition, there are individuals with mild cognitive impairment (MCI), individuals with cognitive decline but not dementia, and therefore cover the spectrum between normal aging and dementia. MCI patients perform 1.5 standard deviations below age-matched controls in memory and other cognitive tests [22].

With age, the incidence and prevalence of dementia increases exponentially [10]. This raises the question: Is dementia inevitable as one ages? In the 1990s, the definition of dementia was described as an age-related or aging-related disorder [23]. The term aging-related suggests that dementia is caused by the ageing process itself. Today, we know that aging without dementia is achievable [24]. Epidemiological studies report that among the 8% who survive to 95 years, half will *not* have dementia [25], suggesting that aging without dementia is achievable [24]. There is a large individual variation in what we refer to as biological age. From neuropathological studies, we know that AD pathology is present in around one-third of old people without dementia, and half of centenarians with dementia do not have sufficient brain pathology to explain their cognitive symptoms [24]. Pathological studies have found a relationship between cerebral atrophy and dementia, but the association between pathological features and dementia diminishes in the oldest old [25, 26].

1.1.8 COGNITIVE RESERVE

Individuals with high cognitive reserve are more resilient to pathological brain changes [27]. For example, epidemiological studies suggest that higher educational attainment is associated with a reduced risk of developing dementia [28]. In addition, individuals with higher cognitive reserves usually have higher test scores and therefore are presumed to be more resilient to AD pathology [27] (Figure 4).

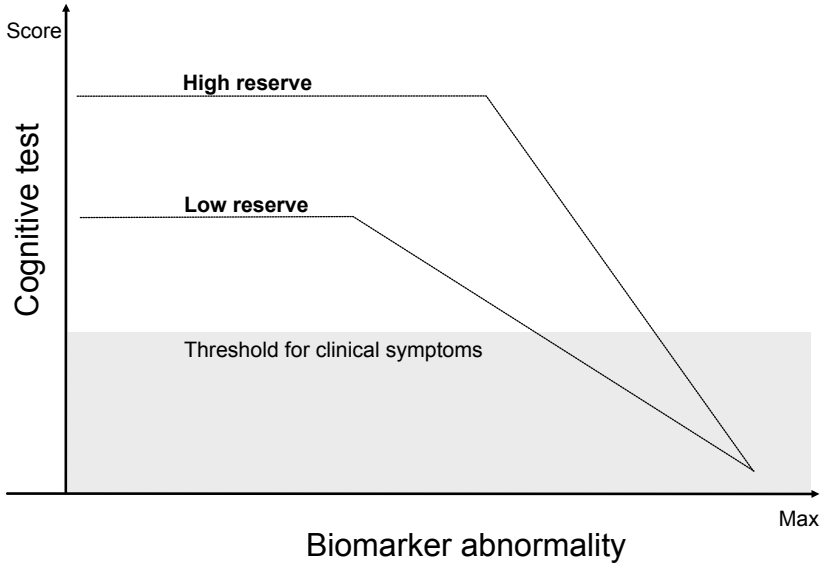

Figure 4. Model of cognitive reserve

Individuals with high cognitive reserve are more likely to perform better on cognitive tests, but at some point, accumulation of dementia pathology affects the cognitive function and results in decline on memory tests. In individuals with high cognitive reserve, the decline appears later in life but, as this model assumes, have a more rapid decline.

Figure acquired and modified from author Stern Y. (2012) [27].

1.1.9 DEMENTIA DIAGNOSES

Dementia is associated with gradually impaired memory and decline in other cognitive functions and ultimately results in disturbance of one's global cognitive abilities. Some cognitive functions are distinguished and reflect the pathological events occurring in the brain with dementia. This section introduces diagnoses of dementia.

1.1.10 CLASSIFICATION

The International Statistical Classification of Diseases and Related Health Problems (ICD) is published by the World Health Organization (WHO) and is the official classification system of diseases in Sweden, which currently uses the ICD-10 classification system. The WHO intends to release ICD-11 in January 2022 [29]. Physicians use this classification system when reporting health data. In psychiatry, the Diagnostic and Statistical Manual of Mental Disorder (DSM) is often used as a classification system because it provides a better way to assess an individual patient's status [30]. The DSM is published by the American Psychiatry Association (APA).

1.1.11 DIAGNOSES IN STUDY I-IV

We used criteria similar to the DSM-III-R [31] in study I-IV for diagnoses of dementia (Table 1). In study I and II, diagnoses of dementia from the Hospital Discharge Register were based on the International Classification of Diseases (ICD)-10 [32]. Diagnoses of dementia from individuals lost to follow-up were established using the Hospital Discharge Register, using ICD-9 and ICD-10.

Table 1. Diagnostic criteria for dementia according to DSM-III-R.
A. Impairment in short-term memory and long-term memory
B. Impairment in at least one of: 1. Abstract thinking 2. Impaired judgment 3. Other higher cortical function disturbances 4. Personality changes
C. A and B significantly interfere with work, social activities or in the relation with others
D. Delirium is excluded
E. Either (1) or (2): (1.) Evidence of an organic factor/-s that is etiologically related to the disturbance, conducted from laboratory tests or physical examinations. (2.) In absence of (1) no nonorganic disorder could account for the cognitive impairment.

Table 1. Diagnostic criteria for dementia according to DSM-III-R

Short-term memory was defined as inability to remember three objects after five minutes. Long-term memory was for example tested by asking patients to name the Swedish Prime Minister who was shot in the mid-1980s (i.e., Olof Palme). Abstract thinking was tested using a common proverb. Higher cortical functions included language impairment (i.e., aphasia), motor impairment (i.e., apraxia), impaired ability to identify and recognize objects (i.e., agnosia), and inability to construct, for example, 3D figures.

Acquired and modified from DSM-III-R criteria for dementia (1987, p. 107) [31].

1.1.12 PREVALENCE WITH DIFFERENT CRITERIA

Since the different classification systems use different criteria, prevalence of dementia differs between different classification systems. Authors who compared the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorder (DSM)-III, -III-R, and -IV and the World Health Organization's International Classification of Diseases 10th revision reported a great (ten-fold) variation between different classification systems [33]. Similarly, in our epidemiological research group (Gothenburg, Sweden) of 1019 elderly we found different prevalence of dementia using different diagnostic criteria [34]: prevalence of dementia was 6.3% using DSM-III-R, 9.6% using DSM-IV, and 3.1% using ICD-10 [34]. Unlike the DSM-IV, the DSM-III-R uses both long-term and short-term memory impairment to diagnose dementia, possibly explaining the differences in prevalence of dementia between the two versions. The lower prevalence of dementia when applying ICD-10 is at least in part explained by the requirement of changes in behaviour or personality for a diagnosis of dementia [34]. The differences in dementia prevalence using different classifications systems is a reason why we exclusively used DSM-III-R similar criteria in all studies in this thesis (see 3.3.1. Diagnoses of dementia).

1.1.13 SEVERITY OF DEMENTIA

When assessing the severity of dementia, we need to consider the individuals decline in cognitive impairment, the disability in their daily life, and disturbances in behaviour.

Different scales can be used to determine the stage of dementia. In this thesis (study I-III), we used the DSM-III-R similar criteria to determine severity of dementia (study IV does not include participants with dementia). Therefore, we describe severity of dementia using only the DSM-III-R criteria.

1.1.14 MCI, MILD, MODERATE, AND SEVERE DEMENTIA

The first stage is mild cognitive impairment (MCI). Nordic studies have found that MCI affects one-third of 70 year olds, with no sex differences [35]. As with dementia, the highest prevalence and incidence of MCI was found in the oldest age group [35, 36].

According to the DSM-III-R criteria, severity of dementia are as follows:

> Mild: Capacity for independent living remains (i.e., personal hygiene is adequate and judgment is relatively intact). Impairment is found in work and social activities.
>
> Moderate: Supervision is necessary but is not needed continually. Independent living is risky.
>
> Severe: Continual supervision is required as minimal personal hygiene cannot be met and patients are unable to explain themselves or are mute.

The stages of dementia presented in Figure 4 show a schematic clinical course in dementia staging. Individuals with mild dementia are able to live an independent daily life, individuals with moderate dementia require daily assistance, and individuals with severe dementia require continuous supervision and care.

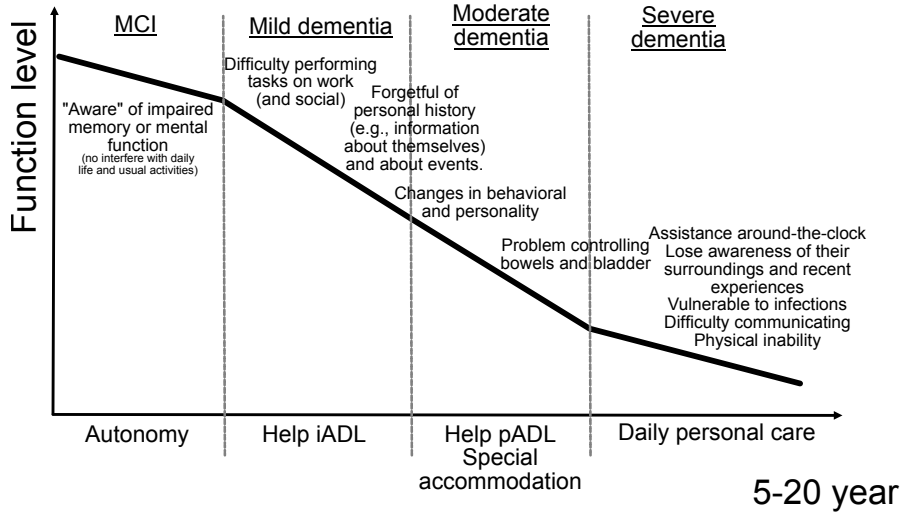

Figure 4. Schematic staging of dementia severity

The activities of daily living (ADL) [37] assessing self-maintenance or functional health. Individuals with MCI had preserved autonomy. Although impairment was found in short memory, changes in personality or reduced orientation were also found with mild dementia, but these people were able to live an independent daily life. With mild dementia he or she may still work, but there may appear situations when there are difficulties in performing specific tasks that previously could be performed. In individuals with mild dementia he or she may need help with more complex skills, with the instrumental activities of daily living (iADL) activities such as cooking, cleaning, laundry, and managing their own finances are included. Moderate dementia required some daily assistance in self-maintenance skills, included in the physical activities of daily living (pADL) are dressing, eating and toileting. Severe dementia required continuous care and supervision [38].

Acquired and modified from Sundelöf J. "Demenssjukdom vid livets slut" Uppsala University Hospital.

1.1.15 SEVERITY ACCORDING TO CLINICAL (DSM-III-R), FUNCTIONAL (ADL), AND COGNITIVE (MMSE) SCALES

Several instruments can be used to measure and classify the extent of impairment in various cognitive domains in individuals developing dementia. The Activities of Daily Living (ADL) includes six basic functions scored from independent to dependent and reflects the daily function of the individual [39]. The Mini-Mental State Examination (MMSE), which measures cognitive impairment using a scale from 0–30 (better performance credit higher scores), is often used as a primary screening instrument for suspected cases of dementia [40, 41].

One study comparing the different stages of dementia severity from a clinical (using the DSM-III-R scale), function (using ADL), and cognitive (using MMSE) perspective found the overall agreement between DSM-III-R criteria and MMSE score to be only 64% and even lower agreement between DSM-III-R and ADL criteria [42]. However, ADL functions are often influenced by conditions other than dementia. These findings highlight the complexity of individual impairment. Therefore, we need to consider many domains when staging dementia.

1.2 SUBTYPES OF DEMENTIA

Between 50 and 75% of people with dementia have Alzheimer's disease (AD) and between 10% and 30% have vascular dementia (VaD), the second most common subtype of dementia [4, 5].

1.2.1 ALZHEIMER'S OR VASCULAR DEMENTIA?

The symptom profile for AD differs from VaD. There are different pathological changes occurring in the brain in AD versus in VaD, resulting in different symptoms [6].

In AD, difficulties with memory as well as difficulties interpreting sensory impressions are especially prominent early in the disease course [4]. In VaD, difficulties with attention, information processing, and executive functioning (e.g., the ability to plan and implement) are especially prominent early in the disease course [5].

In VaD, cognitive changes, especially changes in memory, are much more variously affected than in AD [5]. Therefore, tests such as the MMSE are preferable when examining AD but not VaD patients. Because the underlying pathology in VaD affects the patient's attention, information processing, and executive functions, tests such as the Montreal Cognitive Assessment (MoCA) [43] and Vascular Dementia Assessment Scale (VADAS-Cog) are recommended for screening test in VaD patients [44]. The ICD-10 and DSM-III-R manuals define dementia syndromes, regardless of genesis, as a decline in memory impairment, a symptom profile found in AD but not always pronounced in other subtypes of dementia. The newer DSM-V criteria focus less on memory impairment [45]. There are several other subtypes of dementia with characteristic symptoms. Among the more common: frontotemporal dementia [46], Lewy-body dementia [47] and normal-pressure hydrocephalus [48, 49].

1.3 ALZHEIMER'S DISEASE

This section provides a brief background on the most common subtype of dementia, AD. The pathophysiology behind AD is not fully understood in spite of extensive research efforts over the past two decades. Nonetheless, it has been hypothesised that the start of AD is caused by amyloid β protein deposition in the brain. The processes are described in further detail below.

1.3.1 HISTORICAL BACKGROUND

In November 1901, a woman named Auguste Deter was brought to the city hospital of Mental Ill in Frankfurt, Germany. Mrs. Deter experienced memory and disorientation problems as well as difficulties in writing and reading. Alois Alzheimer, a young doctor at the hospital, enrolled her. When Mrs. Deter died five years later, Dr. Alzheimer autopsied her and later that year presented the autopsy results of Mrs. Deter. In his presentation, Dr. Alzheimer described brain atrophy and two pathological abnormalities [50]. Today, these pathological abnormalities are known as amyloid plaques and neurofibrillary tangles (NFTs). In 1910, the German physician Emil Kraepelin named this mental disease Alzheimer's disease in his textbook [50].

In 1984, George Glenner and Caine Wong described one of Alzheimer's abnormalities as an aggregation of amyloid proteins, later named the amyloid-beta 1-42 (Aβ42) protein [51]. In 1986, hyperphosphorylation of a protein in microtubules was described in AD [52].

1.3.2 HYPOTHESIS OF THE AMYLOID CASCADE

The established hypothesis in Alzheimer's pathophysiology is that toxic Aβ proteins are formed in the brain [53, 54]. Development of toxic Aβ proteins are derived from the amyloid precursor protein (APP) [55, 56]. APP is a membrane protein that is constitutively processed in the brain and regulates the biological activity of the membrane; in the non-pathological process, APP is degraded into small soluble fragments that are easily decomposed [57].

The APP protein can be degraded in different pathways. When APP is degraded by α- and γ-secretase (i.e., the normal non-amyloidogenic pathway), soluble Aβ protein fragments from APP are formed [57], which are considered beneficial to neurons [58]. The clearance mechanism of soluble Aβ proteins is poorly understood, but a majority of fragments are removed through active transport across the blood-brain barrier [59]. In the amyloidogenic process, APP is broken down by β- and γ-secretase (not α-secretase), resulting in insoluble Aβ fragments – especially the 42-based β amyloid protein (Aβ42) is presumed neurotoxic [60] and aggregates into plaques [57, 61] (Figure 5).

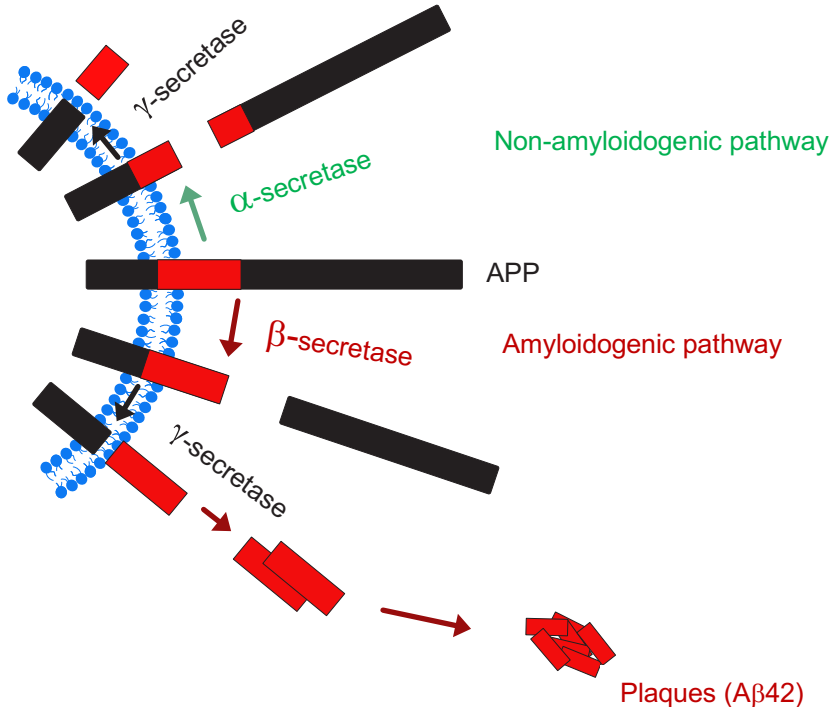

Figure 5. The process of amyloid precursor protein APP.

In the non-amyloidogenic pathway, α- and γ-secretase degrade APP into soluble fragments of APP. In the amyloidogenic process, β- and γ-secretase degrade APP into insoluble fragments of β amyloid protein. The majority of the plaques are aggregated into 40- and 42-amino acid proteins (i.e., Aβ40 and Aβ42). Aβ42 is a core hallmark in AD.

1.3.3 Aβ42 – A CORE HALLMARK IN ALZHEIMER'S DISEASE

According to the latest hypothesis, Alzheimer's begins to develop when insoluble Aβ proteins (especially the Aβ42 protein) start to accumulate in the brain. Aβ42 protein accumulation results in synaptic dysfunction [62], cellular membrane disruption [63], mitochondrial function interference [64], and cytokine activation, which causes inflammation [65]. Moreover, Aβ42 proteins are reported as neurotoxic [60].

1.3.4 TAU PATHOLOGY

The second hallmark of AD is tau pathology. Tau is a protein that stabilizes microtubules and is involved in intracellular transportation [66]. Recent scientific findings suggest that tau is involved in more functions than stabilizing microtubules and intracellular transportation [67]. Total levels of tau (T-tau) in cerebrospinal fluid (CSF) reflect disassembled tau proteins. Both P-tau and T-tau are elevated in the CSF in AD patients. [68, 69].

P-tau

Hyperphosphorylated tau (P-Tau) is significantly higher in patients with AD than in healthy controls [52]. In patients with AD, P-tau levels in CSF correlate with neurofibrillary tangles (NFTs) [70], and NFTs correlate highly to the severity of AD [71], although accumulation of NFTs in the hippocampus are also found in elderly without dementia [72].

T-tau

Total tau (T-tau) levels in CSF reflect neuroaxonal injury. Hence, in other CNS disorders with brain injury (e.g., stroke, head trauma, and Creutzfeldt-Jakob's disease), T-tau levels are also elevated in CSF while P-tau levels remain normal [73]. Some studies have found that levels of CSF T-tau correlate with hippocampal atrophy [74], and some studies have found that hippocampal atrophy is highly correlated with AD [75].

1.3.5 DEVELOPMENT OF ALZHEIMER'S DISEASE

The exact mechanism how Aβ proteins cause clinical symptoms and AD development in humans is still not fully understood. However, recent studies suggest that development of AD is not a linear cascade of events but a multifactorial disease with many interactions [76, 77].

Professor Clifford Jack's 2010 article 'Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade' illustrates the time course from preclinical AD to AD [78]. Accumulation of Aβ42-proteins is the first biomarker to differentiate in CSF, followed by tau pathology. Neurodegeneration determined by MRI is the last biomarker (Figure 6).

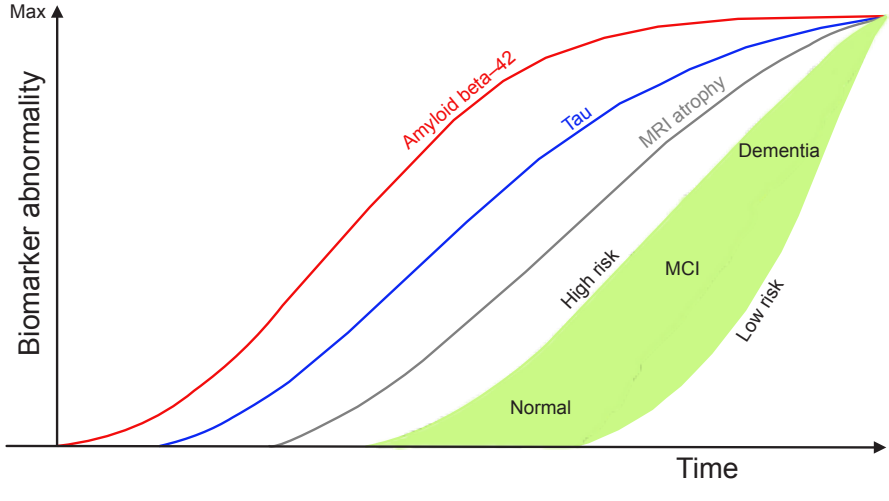

Figure 6. Biomarker model in Alzheimer's disease.

This model illustrates the relation between time (x-axis) and levels of abnormality in biomarkers (y-axis). The red line represents Aβ42, the blue line tau pathology, the grey line neurodegeneration, and the green area cognitive function. The green area represents the individual's reserve capacity.

Acquired and modified from author Jack CR. (2013) [79].

1.3.6 MORTALITY AND ALZHEIMER'S DISEASE

Life expectancy is shortened in individuals with dementia, with estimations of survival after dementia onset between five and nine years [80, 81]. AD, the sixth leading cause of death, accounted for 3.6% of all deaths in the United States in 2014 [82]. The cause of death in AD is not clear, but it is unlikely that AD per se is the reason why a person dies. It is rather vulnerability, especially to infections, that often causes death [82].

The pathological biomarkers for AD (i.e., Aβ42, P-tau, and T-tau in CSF) are presumed to cause and reflect brain atrophy and may affect brain-controlled life essential systems in the body, including balance of electrolytes, energy, appetite, heart function, and blood pressure [83, 84]. Previous reports on mortality and pathological biomarkers in AD were only conducted from clinical studies on patients with manifested AD. These studies report that high CSF T-tau levels was associated with increased mortality [85, 86]. Brain atrophy determined by MRI has previously also been reported to be associated with increased mortality in individuals without dementia [87]. In study II we extend these findings, investigating biomarkers also in individuals without dementia.

1.3.7 ATROPHY IN ALZHEIMER'S SPECIFIC REGIONS

MRI examinations of AD cases reveal that certain brain regions display atrophy. Atrophy in these regions distinguish people with AD from healthy control groups. These regions include the hippocampus and other temporal regions (e.g., the entorhinal cortex, isthmus cingulate, and the inferior and middle temporal gyri) and some posterior brain regions may also be affected in AD (e.g., fusiform, posterior cingulate, and precuneus) [75, 88-94].

1.3.8 GENES AND ALZHEIMER'S DISEASE

This thesis is mainly about late onset sporadic AD. Thus, genetic mutations are only briefly described. However, genetic data provide support for the "amyloid cascade" hypothesis.

Some attention needs to be paid to the *APOE* gene, which provides the instructions for making the fat-binding apolipoprotein E (APOE) protein that transports cholesterol to neurons in the central nervous system [95], transfer APP and Aβ, and controls inflammation, synaptic function and neurogenesis [96-98]. The *APOE* gene is also important in AD [99]. There are three alleles (ε2, ε3 and ε4) of the *APOE* gene, and the most frequent allele is ε3 [95]. Individuals with the ε2 allele seem to have a decreased risk for AD, but individuals with the ε4 allele are at increased risk for AD [23] (and some researchers suggest that this is valid also for VaD [100]). In participants with one or two ε4 allele/-s, levels of AD-biomarkers are suggested to be earlier abnormal (left shifted in Figure 6). On a general population level, dementia symptoms occur earlier in life in ε4 carriers compared to non-carriers [99]. In late onset sporadic AD there is a two- and three-times increased risk for AD with one ε4-allele, and with two ε4-alleles between eight- and twelve-times increased risk for AD compared to without any ε4-allele [98, 101, 102].

Familial AD-cases are rare (constitute <1% of all AD cases [103]), but strengthen the amyloid cascade theory [51]. With a mutation in *APP* (located in chromosome 21), presenilin-1 (*PSEN1*) or presenilin-2 (*PSEN2*) there is an extremely high risk for AD before the age of 65 years [104]. In individuals with Down´s syndrome there is a trisomy of chromosome 21, resulting in an extra copy of *APP*. This overexpression of *APP* leads to increased Aβ-production [105]. Presenilin is a component of γ-secretase [106] that cleaves APP into Aβ-fragments (Figure 5). A mutation in *PSEN1* results in a shift with decreased Aβ40-protein production and increased production of the more neurotoxic Aβ42-proteins [106]. With a PSEN2 mutation the profile is similar to PSEN1 mutations [107, 108], but the Aβ-production is less pronounced [98].

1.4 VASCULAR DEMENTIA

Dementia caused by impaired cerebral blood flow or other cerebrovascular disease is referred to as vascular dementia (VaD). VaD causes between 10% and 30% of all dementia cases [5] and is the second most common cause of dementia [109].

1.4.1 HISTORICAL BACKGROUND

Dr Thomas Willis (1621–1675), described the first patients with VaD, "brain congestion" from stroke and cognitive decline was believed to be caused by hypertension. The common treatment was bloodletting [110]. Dr Otto Binswanger (1852–1929), in cooperation with Dr Alois Alzheimer, divided VaD into four variants [110]: post-stroke dementia, arteriosclerotic brain degeneration, vascular cortical atrophy, and subcortical encephalopathy (also known as Binswanger's disease).

For decades, it was believed that blood vessel blockage as the result of chronic brain ischemia caused dementia. In 1974, Hachinski *et al.*[111] concluded that dementia is also caused by atherosclerosis, so a new concept was introduced – multi-infarct dementia (MID). That is, vascular events that cause dementia are the result of multiple cerebral infarcts. However, multiple cerebral infarcts as the leading cause of VaD was in doubt, especially for vascular-related damage of white matter (i.e., Binswanger's disease) [112]. Finally, a research workshop concluded that VaD was a larger entity than only MID [113]. Today, we believe that there are several vascular mechanisms that can cause cognitive impairment of the VaD type. Hence, there are many types of VaD.

1.4.2 CLINICAL PROFILE IN VAD

In order to simplify the clinical scenario of VaD, there are either a vascular brain injury (e.g., stroke) followed by dementia development or a patient with cognitive difficulties performing brain imaging with findings of vascular brain injury [114]. As VaD may affect different brain regions, different symptoms are manifested. However, VaD is

often associated with impairment in executive functions (e.g., mental slowness and difficulties initiating, planning, and carrying out tasks) [115].

In this thesis, we focus on post-stroke dementia (i.e., thromboses of large vessels) and hypertension as risk factors for VaD, but a brief description of small cerebral vessel diseases and white matter lesions (WMLs) is included in this introduction.

1.4.3 PATHOPHYSIOLOGY

If brain injury from a stroke (ischemic or haemorrhagic) is severe enough, VaD can occur [116]. In addition, small cerebral vessel diseases may also result in VaD; however, small cerebral vessel diseases often go undetected until brain imaging is performed [114]. Stroke and small cerebral vessel diseases impair blood deliver to brain tissue, although cerebral blood vessels have more functions than delivering blood. The blood vessels support brain activities by integrating with neurons, microglia, and astrocytes to maintain integrity of the blood-brain barrier and clear waste products [117-119].

1.4.4 POST-STROKE DEMENTIA

As stroke can cause VaD, risk factors for stroke are also risk factors for VaD – e.g., hypertension [120], diabetes [121], smoking [122], elevated low-density lipoprotein (LDL), and decreased levels of high-density lipoprotein (HDL) [123], as well as atrial fibrillation [124]. During a stroke, cerebral blood vessels can be both haemorrhagic (i.e., rupture of vessels) and ischemic (i.e., thromboses). Clinically, stroke is marked by symptoms that reflect a disturbance in brain function for a duration of $\geq$24 hours. In the 1960s, transient ischemic attack (TIA) was introduced to describe a transient focal neurological deficit with restitution within 24 hours, and TIA diagnoses are made when cerebrovascular aetiology is most likely [125].

It needs to be highlighted that 85% of all strokes are preventable [126]. The two significant highest risk factors for stroke are high age and

hypertension [127]. Hypertension treatments, including changes in life style, are the most important strategies for reducing risk factors for stroke [126]. Implementing treatments and changes in life style is important. Not at least, since within three months after a stroke dementia develops in around 15–30% of all patients and delayed dementia develops in 20–25% [128, 129].

1.4.5 WHITE MATTER LESIONS

White matter lesions (WML) can be the result of many processes and diseases (e.g., vasculitis and hypertension). Although in common is the demyelination and axon loss in subcortical structures, accompanied by narrowing of lumen of the small penetrating arterioles in the white matter [130]. There are different pathological hallmarks in WML: periventricular-WML (i.e., reduced axons and myelin of the white matter near the ventricle wall) and the deep-WML (i.e., the central part of white matter, more widespread in the brain) [130]. The association with impairment in cognitive and functional capacity is probably due to disruption in cortical-subcortical connections [131], especially in the thalamus-cortex connection [115].

One major risk factor for WML is hypertension, which damages the arterioles [132]. The pathophysiology hypothesis is that hypertension causes thickening of the vessel walls, resulting in narrowing of the lumen in the vessels that nourish the white matter, resulting in episodes of hypoperfusion and myelin and axonal loss [133, 134].

1.4.6 HYPERTENSION – A RISK FACTOR FOR DEMENTIA

The WHO defines hypertension as systolic blood pressure (SBP) $\geq$140 mmHg and/or a diastolic blood pressure (DBP) $\geq$90 mmHg [135]. Hypertension results in thickening of blood vessels wall and luminal narrowing, causing a further negative spiral [136]. Hypertension, and especially midlife hypertension, is a risk factor for dementia [137, 138]. As hypertension is a modifiable risk factor, its treatment is essential [139]. Although it is still unclear exactly why hypertension leads to dementia and cognitive decline. It has been hypothesised that

large and small multiple strokes as the result of hypertension indirectly cause dementia [140].

We further need to address the complex relation between BP and dementia. Hypertension, as mentioned above, is an established risk factor for dementia [137, 138]. However, the years before dementia onset BP-levels decline and people with dementia have lower BP than people without dementia of the same age [137], a topic discussed in study III.

1.4.7 ANTIHYPERTENSIVE TREATMENT

This thesis includes studies of participants living in different historical contexts, including the access to improved hypertensive treatments. In 1967 and 1970, the first studies were published reporting less stroke and congestive heart failure when elevated BP was treated [141, 142]. The first study on elderly with hypertension was published in 1986 – European Working Party on High Blood Pressure in Elderly (EWHPE). Before this study, hypertension was considered a component of the aging process [143]. In the EWHPE study, women and men age ≥60 years of age with SBP 160–239 mmHg and DBP 90–119 mmHg were randomised into one group receiving antihypertensive treatment and another group receiving placebo. The group receiving antihypertensive treatment had reduced cardiovascular mortality compared to the placebo group [144]. The Systolic Hypertension in the Elderly Program (SHEP), published in 1991, tested antihypertensive drug treatment in patients with isolated elevated SBP (inclusion criteria were SBP >160 mmHg and DBP <90 mmHg and age >60 years). The results showed reduced incidence of stroke, cardiovascular disease (CVD), and death in participants receiving antihypertensive treatment [145].

Before the Hypertension in the Very Elderly Trial (HYVET) was published in 2008, some studies suggested that BP and death were inversely related in the very old [146]. However, the HYVET study found that antihypertensive treatment in participants >80 years with an SBP >160 mmHg was more beneficial than in any other age group (30% reduction in stroke, 21% reduction in death from any cause, 23%

reduction in the rate of death from CVD, and a 64% reduction in heart failure) [147].

Participants in study I–III who were born between 1901–09 were between 77 and 85 years old when the EWHPE study was published, which confirmed that people >60 years old with an SBP/DBP ≥160/90 mmHg benefit from antihypertensive treatment. In study III there were two cohorts. The later cohort were born 1923–24 and examined (2008-10) simultaneously with the publication of the HYVET study.

1.5 MIXED DEMENTIA

Mixed dementia is most often a combination of vascular components and Alzheimer's pathology [148]. This condition is common, and in some studies estimated to account for approximately 30–40% of all dementia cases [149, 150]. A neuropathological review from 2002 reported that mixed dementia accounts for 20–40% of all dementia [151]. Neuropathological studies are important since the prevalence of mixed dementia may be underestimated [152, 153].

1.5.1 POTENTIATING PROGRESS

Exactly how vascular risk factors increase the rate of cognitive decline in AD (and vice versa) is unclear, but there are probably many explanations. Previous studies found that small infarcted brain tissues amplifies the effect of AD on cognitive decline, and clinical expression of AD is enhanced by asymptomatic brain injury from VaD [154]. Interestingly, one author claims that AD is primarily a microvascular disease because degeneration of capillaries in the hippocampus is a central pathophysiological event in AD [155].

1.5.2 CEREBRAL AMYLOID ANGIOPATHY

How AD pathology affects the vascular system may seem difficult to explain, although one explanation is cerebral amyloid angiopathy (CAA). CAA occurs when the Aβ protein accumulates on the walls of cerebral and meningeal blood vessels [156]. Accumulation of Aβ within the walls of cerebral capillaries contributes to brain hypoperfusion and ischemia [156] and this may further stimulate Aβ production [157, 158]. Of clinical importance is also the enhanced risk for haemorrhagic stroke with CAA [159].

1.5.3 OLDER INDIVIDUALS WITH DEMENTIA

In people >80 years of age, mixed dementia is not the exception; some studies report mixed dementia in older individuals as the norm [5].

Older individuals with dementia often have both a vascular component and Alzheimer's pathology with amyloid-ß accumulation in the brain [8, 26, 160]. Amyloid-ß accumulation in the brain increases with both advancing AD [161] and higher age [162]. Patients with higher amyloid-ß load also have lower cerebral blood flow in several brain regions, especially in the hippocampus [163]. Lower cerebral perfusion is also related to accelerating cognitive decline and risk of dementia development [164]. In relation to this, previous reports have found that high BP in younger years is a risk factor for development of dementia in later life [165].

2 AIM

The overall aim of this thesis is to further expand the understanding of risk factors (e.g., stroke and hypertension) for VaD and AD in older individuals and biomarkers for AD.

Specific aims of each study

Study I examines the prevalence of stroke, transient ischemic attack (TIA), and dementia in the oldest old (97-year-olds) and explores the relationship between stroke/TIA and dementia in the oldest old.

Study II investigates whether levels of biomarkers for AD in CSF (Aβ42 and T-tau) in 85-year-olds are associated with survival and whether this association remains independent of dementia status. Furthermore, this study estimates the relationship between AD biomarkers in CSF and dementia development.

Study III investigates changes in BP in 85-year-olds from two different birth cohorts, who were examined 22 years apart. In addition, study III explores whether BP levels remained lower in participants with dementia also in the later examined cohort.

Study IV examines whether hypertension is associated with brain atrophy in Alzheimer's specific brain regions in 70-year-olds without dementia, using magnetic resonance imaging.

3 METHOD

In this section, I briefly describe examinations relevant for study I-IV. All the studies conducted for this thesis were part of the Gothenburg H70 Birth Cohort Studies (Table 2).

3.1 THE GOTHENBURG H70 BIRTH COHORT STUDIES

The Gothenburg H70 Birth Cohort Studies are multidisciplinary epidemiological population-based studies including different birth cohorts followed for many years (e.g., The Population Studies of Women [166], which began in 1968 and is ongoing, with more than 50 years follow-up). Our aim is to study both somatic and mental health on representative birth cohorts of the population in Gothenburg, Sweden. The cohorts for the H70 studies were selected using the Swedish Tax Agency's register, which supplied information of birth and address.

The Gothenburg H70 Birth Cohort Studies include a comprehensive survey: psychiatric, cognitive, and physical health examinations, self-reported questionnaire data, examination of blood and cerebrospinal fluid, genetic and family histories, medications, social factors, functional ability and disability, physical fitness and activity, body composition, lung function, audiological and ophthalmological examinations, and neuroimaging data, which have been described in detail previously [8, 167]. There is an attempt to make the examinations of the different cohorts to be identical between studies, so that comparisons between different birth cohorts and examination years can be made. However, with medical progress, new and modern assessments have been added to the examinations. Information about the H70 study design has been previously described in detail in the H85-study in 1986–87 [8], and the H70 study for 2014–16 [167].

3.1.1 EXAMINED IN THIS THESIS:

Table 2. The Gothenburg H70 Birth Cohort Studies

Participants in study I–IV are marked with grey squares.

Participants age are presented in the square. In the x-axis examination year and in the y-axis participants birth year. Participants are followed over time.

Study I
All 973 participants (817 women and 156 men) who were 97-years-old and living in Gothenburg, Sweden and born between 1 July 1901 and 31 December 1909 were invited to this study. This is a follow-up study of the 95+ study. Of the 973 invited participants, 62 could not participate (48 died before they could be contacted, eight could not speak Swedish, four lived abroad, and two could not be traced), resulting in 911 eligible participants. Of these, 591 (484 women and 107 men) accepted to participate (64.9% response rate). The examinations were conducted between 1998 and 2007.

Study II
All 85-year-olds born between 1 July 1901 and 30 June 1902 in Gothenburg, Sweden were invited to participate in a health survey (n=1502). A systematic subsample was selected for a psychiatric examination (n=826). Of these, 43 died before examination (effective sample n=783), 14 moved or could not be traced, 229 declined to participate, and 46 only participated in part of the study. The final study population contained 494 participants (63.1%) – 351 women and 143 men. Study II included a subsample of the first 165 participants who were invited to undergo a lumbar puncture (LP). Sixty-nine accepted (41.8% response rate).

Study III
In study III, 85-year-olds born 1923–1924 were compared to 85-year olds born 1901–1902. The 1901–02 cohort is described above in study II. In the cohort of 85-year-olds born 1923–24, every second 85-year-old in Gothenburg, Sweden born between 1 July 1923 to 30 June 1924 was invited to the examination in 2008–10 (n=1013). Of these 40 died before the examination, 19 could not speak Swedish, four had emigrated, and six could not be traced, leaving an effective sample of 944 individuals, of which 571 participated (response rate 60.5%; 212 men and 359 women).

Study IV

In study IV, the participants came from the Gothenburg H70 Birth Cohort Study 2014–16; all women and men born in 1944 on specific dates (birth dates ending with 0, 2, 5 or 8) living in Gothenburg were invited to participate (n=1667, 894 women and 773 men). Of these, 1203 agreed to participate (response rate 72.2%; 644 women and 559 men). All participants were invited to magnetic resonance imaging (MRI) examination, 822 accepted and in 791 participants (414 women and 377 men) a complete MRI was performed.

3.2 EXAMINATION

The studies include a general and an additional examination. The additional examination of importance in this thesis includes an LP to obtain CSF, brain MRI scan and close informant interviews.

3.2.1 INVESTIGATOR

All participants were examined by trained psychiatric research nurses, supervised by neuropsychiatrists, psychiatrists, or geriatric neuropsychiatrists. Interviews were structured but allowed for clarifying questions.

3.2.2 ADDITIONAL EXAMINATION

Cerebrospinal fluid
In study II, the first 165 participants were invited to undergo LP and 69 accepted (41.8%). The LP was performed in the L3–4 or L4–5 interspaces. All LPs were performed in the morning, and 12 mL of CSF was collected in polypropylene tubes. There were no reports of serious adverse events.

All CSF samples were analysed at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Mölndal, Sweden using a sandwich enzyme-linked immunosorbent assay (ELISA) to identify and quantify Aβ40, Aβ42, T-tau, and P-tau. The biochemical analyses were performed by certified laboratory technicians who were blinded concerning both clinical information and eventual diagnoses of the participants. After the analyses, the remaining CSF was stored at −80 °C for later analyses.

Magnetic resonance imaging

Participants who agreed to a MRI (n=822) in the H70-study (study IV) were interviewed before they underwent the MRI examination. In five cases, there were contraindications that excluded them from taking part in a MRI. In 26 cases, MRI imaging was interrupted because of claustrophobia and/or noise discomfort. Of the participants who agreed to a MRI, 791 (96.2%) completed the MRI examination. A 3.0T Philips Achieva MRI at the Aleris Clinic in Gothenburg was used. To generate divided brain regions, FreeSurfer version 5.3 was used. In 50 cases, there was a processing error (e.g., movements and anomalies), resulting in a total sample of 741 individuals (90.1% of participants agreed to a MRI, 386 women and 355 men).

In study IV, we hypothesised that atrophy in Alzheimer's specific brain regions was driven by hypertension. In order to investigate this, we needed to normalize the investigated regions (i.e., the Alzheimer's specific brain regions). Specific brain volume correlated with intracranial volume (ICV), but are not scale proportionally with the ICV [168]. We also needed to considered sex differences (in men the ICV is 10–12% larger) and inter-individual variability in ICV [169, 170]. Our methods for adjusting specific brain volume with ICV have been previously described [168]. Since we only examined 70-year-old participants, we did not need to consider the age differences in brain volumes.

Close informant interview

Participants were asked for permission to interview a close relative or key informant (e.g., husband/wife, brother/sister, child, cousin, close friend, or caregiver). Key informant interviews were performed by a registered nurse or a physician, both with experience in psychiatry, over the telephone. The interviews were semi-structured and included questions about changes in intellectual function and/or behaviour. Questions about any psychiatric symptoms and the daily self-care activities were framed and also somatic symptoms and potential risk factors were asked for. In cases where the participant had developed dementia, questions about age, symptoms at onset, and course were asked.

Registers
In study I, information about stroke or TIA and dementia was obtained from The Swedish Hospital Discharge Register. This register uses the ICD classification system for every person admitted to a Swedish hospital. The Swedish Population Register includes all deaths in Sweden. In Sweden, a physician has to sign the death certificate before any funeral services can take place. In study I and II, date of death was retrieved from the Swedish Death Register.

Lost to follow-up
For individuals lost to follow-up, a diagnosis of dementia was based on the Swedish Hospital Discharge Register and medical records. The medical records were evaluated by geriatric neuropsychiatrists.

3.3 DIAGNOSES AND STATISTICS

In this chapter, the method for diagnoses of dementia, subtypes of dementia, and stroke are described. Further, my work in study I-IV and in the Gothenburg H70 Birth Cohort Study are described. Last, a summary of statistics used in study I-IV is described.

3.3.1 DIAGNOSES OF DEMENTIA

The participants in study I-IV were diagnosed with dementia using criteria similar to those found in the Diagnostic and Statistical Manual of Mental Disorder, IIIrd edition, revised (DSM-III-R) [31]. In our study, however, we accepted short-term *or* long-term memory as diagnostic criteria for dementia (in contrast to DSM-III-R, where short-term *and* long-term memory are the criteria). We used an algorithm to collect data from our examinations. Information of symptoms with levels causing significant difficulties in social functioning from both the personal examination and the interview with a key informant (considered separately) were used to diagnose participants with dementia. When an interview with a key informant was not available, a dementia diagnosis was made according to the psychiatric examination, if clear symptoms of dementia were present. In borderline cases, participants were diagnosed with dementia if an obvious decline in cognitive function that interfered with the patient's daily activities and social function were evident according to a key informant. In uncertain cases, at least two geriatric psychiatrists discussed and jointly determined if the individual should be diagnosed with dementia or not.

3.3.2 DIAGNOSES OF SUBTYPES OF DEMENTIA

Based on information from the personal examination, the interview with a key informant, medical records, and the Swedish Hospital Discharge Register were used to determine the etiologic subgroup of dementia. The dementia subtypes were determined by geriatric neuropsychiatrists. The AD subtype was diagnosed according to criteria similar to those in the National Institute of Neurological and

Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [171] (NINCDS-ADRDA). In summary, the criteria included progressive impairment of memory and cognitive functions without sensory or motor deficits in the early stages of the disease. Laboratory tests are required to exclude other causes of dementia [172]. One guide proposes the use of the terms probable, possible, and definite AD [173].

VaD was diagnosed according to criteria similar to those in the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherce et l´Enseignement en Neurosciences [113] (NINDS-AIREN). That is, VaD was diagnosed when there was a clear relationship (within one year) between neurological symptoms (e.g., hemiparesis or motor aphasia) and the first symptoms of dementia.

Other dementias were diagnosed when other factors were likely to be the cause.

3.3.3 STROKE AND TRANSIENT ISCHEMIC ATTACK

In study I, the stroke/TIA diagnoses were obtained from self-reports, key informants, and the Hospital Discharge Register. The interviews with participants and key informants included questions about sudden onset of focal symptoms such as hemiparesis or acute aphasia, symptom duration, age at stroke/TIA, and admission to hospital due to stroke/TIA. All information from the interviews, including side notes, was evaluated by two of the authors: Ingmar Skoog and Mats Ribbe. Only in cases with definite history of acute focal symptoms (i.e., hemiparesis or aphasia) diagnosis was made.

3.3.4 CONTRIBUTION OF WORK

As a doctoral student, I developed my ability as a researcher and deepened my understanding of my research field. In collaboration with my supervisors, I initiated the research hypotheses and designed the studies. As a first author of study I-IV, I had the main responsibility to

actively correct underlying data of study I-IV. I received help from a statistician in some analyses, but the majority of statistical analyses I performed myself. Afterwards I interpreted the results and wrote the draft, which was reviewed by my supervisor and co-authors, I had the responsibility of submitting the text for publication and was the corresponding author. I was responsible for the review process.

In our studies, we examined older individuals with a comprehensive battery of somatic (e.g., blood samples including haemoglobin, cholesterol, glucose, and creatinine as well as ECG, BP measurements, and a neurologic examination), psychiatric, and neuropsychiatric tests. After the examination, all participants were informed about their test results. In many participants, the tests discovered unexpected pathological findings that needed medical attention (e.g., untreated high BP, pathological laboratory results, and atrial fibrillation). A few severe diseases required immediate medical attention. Together with other licensed physicians, I had the responsibility to interpret the examination results, inform the participants of their results, and, when required, ensure that they received medical care (e.g., admission to emergency or other departments at the Sahlgrenska University Hospital). This procedure was used in the 2014-16 examinations on 70-year-old participants (study IV), and in 85-year-old participants born 1930, examined 2015. In addition, during my time as a doctoral student, I lectured and educated colleagues at the medical program at the University of Gothenburg.

3.3.5 STATISTICS

In study I, the proportions of participants with a history of stroke/TIA and dementia were tested with Fisher's exact test, which was reported as odds ratios (OR) and 95% confidence interval (CI). Differences in means, such as mean age at stroke and dementia onset, were tested with the Independent t-test. The two-year mortality and living in an elderly care home/institution were tested with logistic regression analysis in order to allow multiple explanator variables simultaneously. In our model, explanatory variables were stroke/TIA, dementia and sex, and outcome was two-year mortality in one model and living in an institution in the other (OR and 95% CI were reported).

In study II, baseline characteristics of participants with and without dementia were compared with the Independent t-test, Chi-square test and Analysis of Variance (ANOVA). Spearman's rank correlation and Pearson's correlation were used to investigate the relation between levels of CSF Aβ42 and T-tau at 85-years age and age at death. The R^2 line for Pearson's correlation between age at death and CSF biomarkers was reported. In order to explore if dementia status affected the relation between age at death and levels of CSF biomarkers, the slope difference between participants without dementia during follow-up, dementia development onset during follow-up, and dementia at baseline, was examined with a linear mixed-effect model. Participants were divided into tertiles based on CSF Aβ42/T-tau ratio (independent of dementia status). The tertiles in relation to years of survival were presented with a Kaplan-Meier curve. Years of survival were defined as the time from baseline examination to the date of death.

In study III, baseline characteristics of participants examined 1986–87 and participants examined 2008–10 were compared with the Chi-square test and Independent t-test. Mean BP differences between examinations, sexes and dementia status groups were examined with the Independent t-test. Proportion of participants with a (1.) BP ≥140/90 mmHg, (2.) antihypertensive treatment or (3.) hypertension (i.e., ≥140/90 mmHg and/or antihypertensive treatment) in the two examinations (1986-87 *versus* 2008-10), and in relation to dementia status, were examined with the Chi-square test.

In study IV, baseline characteristics were examined with the Chi-square test and Independent t-tests. MRI imaging was processed with FreeSurfer in order to generate divided brain regions. The volume from eight previously reported Alzheimer's specific brain regions [75, 88-94] were selected for analyses (hippocampus, entorhinal cortex, inferior-, and middle temporal gyri, isthmus cingulate, fusiform, posterior cingulate and precuneus). Due to sex differences and individual variation in ICV we adjusted the raw volume in those eight Alzheimer's specific brain regions using a previously established normalization method [168]. Shortly, the deviation from the regression line between the Alzheimer's specific brain regions (e.g., hippocampus raw volume) and the total ICV generated a residual. This residual was

then used to adjust the mean raw volume of interest. Independent t-test was then used to compare the adjusted mean volume between normotensive participants without a history of antihypertensive treatment and participants with different forms of hypertension and/or antihypertensive treatment.

3.4 ETHICAL APPROVAL

The studies in this thesis were approved by the Regional Ethical Review Board in Gothenburg. Written informed consent was obtained from all participants except when participants were blind (oral informed consent was provided) or when participants had a severe diagnosis of dementia (close relatives provided consent). All procedures with human participants were done following the ethical standards of the amendments of the original 1964 Helsinki Declaration.

In study I, the ethics committee includes the Approval Numbers (AN): R175-98. This is a part of the 95+ study (AN: 349-96, extended S117-98). However, the origin of the participants were from the H70-study initiated in year 1971 (with the responsibility number 52).

Study II was part of the original H70 study, but with an additional approval – acceptance of a lumbar puncture (AN: 340-86) – and the participants were followed until death: 88, 90, 92, 95, 97, 99, 100, 101, and 102 years old (the last participant in this sub-sample accepting a lumbar puncture died a few months after reaching 101 years old). Ethical approval includes the following: 89-04-28 (AN:123-89), 90-09-20 (AN: 263-90), 91-03-20, 91-10-07, 92-11-11 (S102-92), 96-06-19 (AN: 349-96), and 96 06 19 (AN: 349-96, extended S 117-98, AN: R175-98, extended T 378-02). The follow-up study after the age of 99 years was approved as AN: (S 328-00, extended AN: T 378-02).

In study III, there is a comparison between 85-year-olds born 1901–02 and born 1923–24. The ethical approval for this study is AN: 607-08. The ethical approval for the 1923–24 cohort is AN: 783-11.

In study IV, participants born in 1944, all aged 70 years, were examined between 2014 and 2016. The ethical approvals (AN) for this study are as follows: 869-13, T076-14, T166-14, 976-13, 127-14, T936-15, 006-14, T703-14, 006-14, T201-17, T915-14, 959-15, and T139-15. In addition, the Radiation Protection Committee with (AN 13-64) also approved this study.

Information was also obtained from different agencies in Sweden: Swedish National Quality Registries (cardiovascular diseases, dementia, diabetes, fractures, and stroke); the Swedish Cancer Register; the Cause of Death Register, the Swedish Prescribed Drug Register; and the Register for Care and Social Services. In addition, information was obtained on primary care, hospital care, and specialist care within and outside the Region of Västra Götaland. In this thesis, ethical application for disclosure of information from registers was approved (Dnr: 5.2.1-40729/2014).

4 RESULTS

Complete reprinted publications and articles are attached at the end of the thesis.

In summary, the main results;

Study I reported a high prevalence of dementia and stroke in the oldest old. In the oldest old, however, a previous stroke history did not increase the risk for later development of dementia as much as in younger age groups.

Study II reported that levels of AD biomarkers (Aβ42 and T-tau) in CSF was associated with differences in survival in 85-year-olds, and CSF Aβ42 levels were related to three-year incidence of dementia.

Study III, comparing two cohorts of 85-year-olds, found that BP was lower in the later examined cohorts. Participants with dementia had lower BP than participants without dementia in both cohorts. However, hypertension was found in almost half of all 85-year-olds with dementia in the later examined cohort.

Study IV showed that hypertension was associated with reduced volume in some Alzheimer's specific brain regions in 70-year-old participants without dementia. In participants receiving a hypertension diagnosis more than ten years before the study, volume reduction in Alzheimer's specific brain regions was more pronounced.

4.1 STUDY I: STROKE AND DEMENTIA IN THE OLDEST OLD

A Population-Based Study on Dementia and Stroke in 97 year olds [160].

Mats Andersson*, Xinxin Guo, Anne Börjesson-Hanson, Martin Liebetrau, Svante Östling, Ingmar Skoog.
(*Andersson, today Ribbe).

Prevalence

In the oldest old (97 years), dementia was found in more than half of all participants (54.5%). Stroke/TIA history was found in about one-fifth (21.5%, Figure 7).

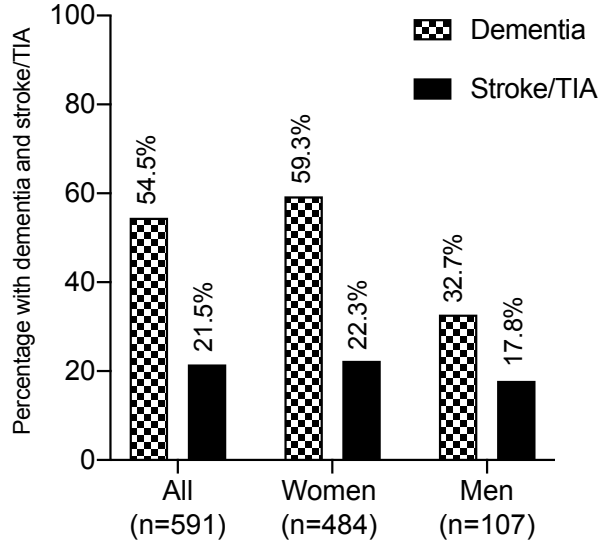

Figure 7. Prevalence of dementia and stroke/TIA

Dementia was found in more than half of all women (59.3%) and almost one-third of all men (32.7%) among the oldest old. A stroke/TIA history was found in 22.3% of women and in 17.8% of men. With permission from Oxford University Press.

With a history of stroke/TIA, dementia was more common than in those without a stroke/TIA history (65.4% and 51.5%, respectively; $p<0.01$), and there is an almost two-fold increase in risk for dementia with stroke/TIA history (OR 1.8, 95% CI: 1.2-2.7). In women with dementia, 70.4% had history of stroke/TIA. In men with dementia,

36.8% had history of stroke/TIA. A history of stroke/TIA was related to dementia in women (OR 1.9, 95% CI: 1.2-2.9), but not in men (OR 1.2, 95% CI: 0.4-3.5).

Consequences

The two-year mortality was 67.7% in participants with dementia and 34.9% in participants without dementia (OR 3.9, 95% CI: 2.8-5.5). The two-year mortality was 62.2% in participants with a history of stroke/TIA and 50.2% in participants without a history of stroke/TIA (OR 1.6, 95% CI: 1.1-2.4).

In the oldest old, 63.4% of women and 31.7% of men were living in an elderly care home/institution. Dementia was associated with living in an elderly care home in both women (OR 11.1, 95% CI: 7.2-17.2) and men (OR 19.0, 95% CI: 6.7-53.5). Participants with a history of stroke/TIA were also more likely to live in an elderly care home//institution (OR 1.7, 95% CI: 1.1-2.6), However, in a logistic regression with dementia, stroke/TIA and sex, a history of stroke/TIA did not significantly correlate to two-year mortality or living in an elderly care home (Table 3).

Table 3. Two-year mortality and living in an elderly care home/institution in relation to dementia, stroke/TIA and sex in a logistic regression analysis

(n=591)	Two-year mortality OR (95% CI)		Institution OR (95% CI)	
Dementia		**4.3 (3.0-6.1)***		**11.9 (7.9-17.8)***
Stroke/TIA		1.4 (0.9-2.2)		1.4 (0.8-2.3)
Sex	*Male*	**1.8 (1.2-2.9)***	*Female*	**1.9 (1.2-3.3)***

Table 3. Consequences of dementia and stroke/TIA

Two-year mortality was related to dementia and male sex. Living in an elderly care home/institution was related to dementia and female sex.

*Statistical analyses: Logistic regression analysis including dementia, stroke/TIA and sex. *p<0.05 was considered statistically significant. With permission from Oxford University Press.*

Printed with permission from Oxford University Press.
Andersson M, Guo X, Börjesson-Hanson A, Liebetrau M, Östling S, and Skoog I.
A Population-Based Study on Dementia and Stroke in 97 year olds
Age & Ageing 2012;41: 529-533. doi: 10.1093/ageing/afs040

4.2 STUDY II: CSF MARKERS AND SURVIVAL

Amyloid β42 and Total Tau Levels in Cerebrospinal Fluid Associate with Survival in an 85-Year-Old Population-Based Cohort Followed until Death [162].

Mats Ribbe, Silke Kern, Anne Börjesson-Hanson, Svante Östling, Henrik Zetterberg, Kaj Blennow, Ingmar Skoog.

Mortality

Participants with high levels of CSF Aβ42 (Pearson's correlation 0.359 (p<0.01) or low levels of CSF T-tau (Pearson's correlation −0.333, p<0.01) had prolonged survival. Participants were divided into three categories, based on high-, intermediate-, and low-ratio of CSF Aβ42/T-tau levels. Participants with a high ratio (i.e., high CSF Aβ42 level and a low CSF T-tau level) survived more years compared to participants in the intermediate- or low-ratio group (Figure 8).

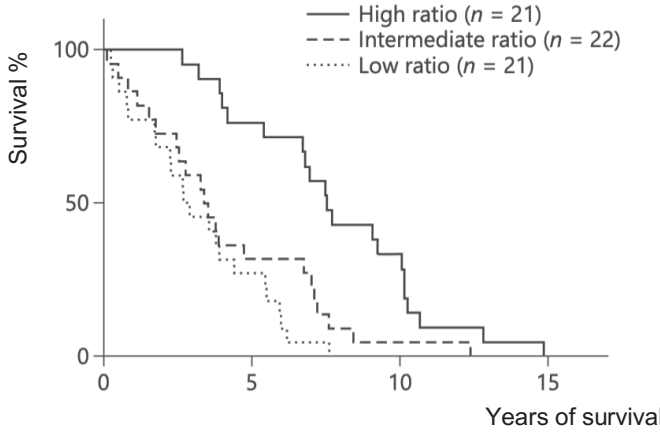

Figure 8. Ratio of CSF Aβ42/T-tau and survival

Unrelated to dementia status, the one-third with the lowest ratio (i.e., low CSF Aβ42 and high CSF T-Tau) survived shortest (····· line) and the one-third with the highest ratio (i.e., high CSF Aβ42 and low CSF T-Tau) survived longest (—line).

Statistical analyses: Kaplan-Meier. With permission from S. Karger AG, Basel.

Dementia development in relation to CSF biomarkers

Lower CSF Aβ42 was related to three years incidence of dementia. Participants with dementia at baseline had lower CSF Aβ42 and higher CSF T-tau than participants who did not develop dementia (Table 4).

Table 4: CSF biomarkers in participants without dementia develop *versus* with baseline dementia or with dementia development.

	n	CSF Aβ42 (pg/mL)	CSF T-tau (pg/mL)
No dementia development – mean	23	**669.8**	**161.0**
Baseline dementia – mean	29	**408.6****	**243.0****
Development of dementia <88 years – mean	7	**415.6***	190.6
Development of dementia >88 years – mean	6	594.7	184.4

Table 4. CSF biomarkers with vs. without dementia

*Participants with dementia at 85-years age (baseline) had lower CSF Aβ42 (408.6 pg/mL vs. 669.8 pg/mL, **p<0.001) and higher CSF T-tau (243.0 pg/mL vs. 161.0 pg/mL, **p<0.001) than participants who did not develop dementia during follow-up. Participants who developed dementia within three years had lower CSF Aβ42 than participants who did not develop dementia during follow-up (415.6 pg/mL vs. 669.8 pg/mL, *p<0.05).*

Statistical analysis: Independent t-test. With permission from S. Karger AG, Basel.

Printed with permission from S. Karger AG, Basel.
Ribbe M, Kern S, Börjesson Hansson A, Östling S, Zetterberg H, Blennow K, Skoog I.
Amyloid β42 and Total Tau Levels in Cerebrospinal Fluid Associate with Survival in an 85-Year-Old Population-Based Cohort Followed until Death.
Dement Geriatr Cogn Disord 2019;47:114-124. doi: 10.1159/000499066

4.3 STUDY III: BLOOD PRESSURE AND DEMENTIA

Time Trends in the Relation Between Blood Pressure and Dementia in 85-year-olds.

Mats Ribbe, Silke Kern, Hanna Wetterberg, Lina Rydén, Anna Zettergren, Xinxin Guo, Ingmar Skoog.

This section contains unpublished results and therefore is condensed. For more information, see **Appendix III**.

Time trends

Among 85-year-olds examined 2008–10 compared to 85-year-olds examined 1986–87, body mass index (BMI) was higher ($p<0.05$), smoking was more common ($p<0.001$), stroke prevalence was higher ($p<0.001$), as well as prevalence of myocardial infarction ($p<0.05$) and diabetes ($p<0.05$). Despite this, the SBP was 18.1 mmHg lower ($p<0.001$) and the DBP was 6.8 mmHg lower ($p<0.001$) in 85-year-olds examined 2008–10 compared to 85-year-olds examined 1986–87.

Dementia

In 85-year-olds examined 2008–10, participants with dementia had 7.5 mmHg lower SBP than participants without dementia ($p<0.001$). The DBP was not significantly lower ($p=0.105$). In 85-year-olds examined 1986-87, participants with dementia had 13.5 mmHg lower SBP ($p<0.001$) and 2.8 mmHg lower DBP ($p=0.028$) than participants without dementia (Figure 9).

Almost half of 85-year-olds examined 2008–10 with dementia had an SBP/DBP $\geq$140/90 mmHg.

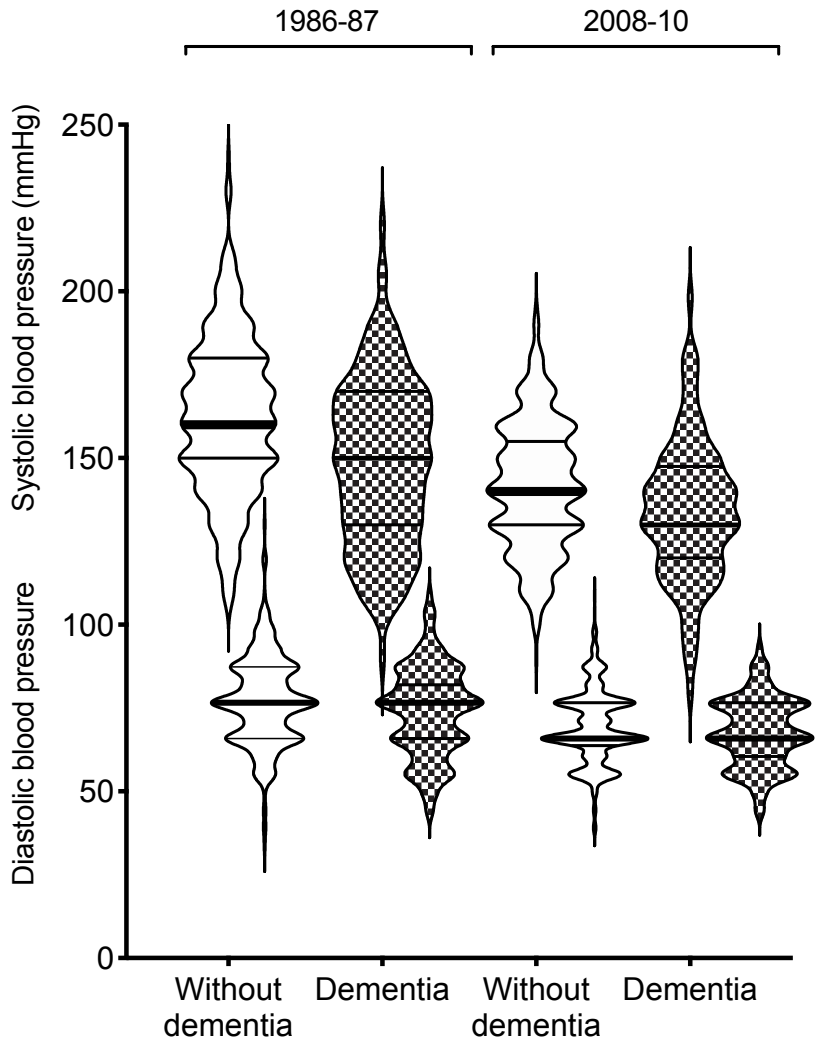

Figure 9. Blood pressure levels with and without dementia

In 2008-10, examination participants with dementia had –7.5 mmHg SBP and –1.9 mmHg DBP than participants without dementia.

In 1986-87, examination participants with dementia had –13.5 mmHg SBP and –2.8 mmHg DBP than participants without dementia.

Statistical analyses: Independent t-test. Presented: Violin plot (lines at the median and lower and upper quartile).

4.4 STUDY IV: HYPERTENSION AND ALZHEIMER BRAIN ATROPHY

The Effect of High Blood Pressure on Alzheimer's Specific Brain Regions.

Mats Ribbe, Silke Kern, Olof Lindberg Alejandra Machado, Eric Westman, Henrik Zetterberg, Kaj Blennow, Anna Zettergren and Ingmar Skoog.

This section contains unpublished results and therefore is condensed. For more information, see **Appendix IV**.

In 132 of the 70-year-olds without dementia who performed a MRI, a physician had diagnosed hypertension at least ten years before the study. At the 70-year-olds' examination, an SBP/DBP $\geq$140/90 mmHg was found in 402 participants. Normotensive BP and no history or current antihypertensive treatment was found in 215 participants.

Compared to normotensive participants with no history of antihypertensive treatment, participants with hypertension more than ten years had smaller volumes in both hemispheres of the hippocampus, isthmus cingulate, middle temporal gyri, and in the left hemisphere of entorhinal cortex and in the right hemisphere of inferior temporal gyri (Table 5). In participants with an SBP/DBP $\geq$140/90 mmHg at examination, both hemispheres of isthmus cingulate, the middle temporal gyri, and in the right posterior cingulate were smaller compared to normotensive participants with no history of antihypertensive treatment (Table 5).

A subsample of 279 participants, having performed a MRI, underwent a LP. Levels of Aβ42, T-tau, and P-tau in CSF did not differ between normotensive participants without history of antihypertensive treatment compared to participants with a diagnosis of hypertension of more than ten years or an SBP/DBP $\geq$140/90 mmHg at examination.

Table 5. Alzheimer's specific brain volumes and cerebrospinal fluid markers in normotensive and hypertensive participants.

	Normotensive BP (n=215)		**≥140/90 mmHg** (n=402)		**Hypertension >10 years** (n=132)	
Brain hemisphere:	Left	Right	Left	Right	Left	Right
Hippocampus ≈	**3,900 mm³**	**4,000 mm³**	–0.5%	–0.1%	**–4.5%*** **	**–4.0****
Temporal regions:						
Entorhinal cortex ≈	**1,850 mm³**	1,600 mm³	–1.5%	–0.1%	**–4.5%***	–3.5%
Inferior temporal ≈	10,000 mm³	**9,550 mm³**	1.0%	–0.5%	–1.0%	**–3.0%***
Isthmus cingulate ≈	**2,500 mm³**	**2,300 mm³**	**–2.5%***	**–3.0%****	**–3.5%***	**–5.0%***
Middle temporal gyri ≈	**9,800 mm³**	**10,700 mm³**	**–2.5%****	**–2.0%***	**–4.0%*** **	**–3.5%****
Posterior regions:						
Fusiform ≈	9,400 mm³	9,000 mm³	–0.5%	–1.0%	–1.5%	–2.0%
Posterior cingulate ≈	2,900 mm³	**3,000 mm³**	–1.5%	**–2.0%***	–1.5%	–1.5%
Precuneus ≈	8,500 mm³	8,800 mm³	0.5%	0.5%	–0.5%	–1.0%

Table 5. Hypertension in relation to brain atrophy

In participants who received a diagnosis of hypertension more than 10 years before the study, the volume was smaller bilaterally in the hippocampus, isthmus cingulate, middle temporal gyri, and in left hemisphere of entorhinal cortex compared to normotensive participants (i.e., SBP <140 mmHg and DBP <90 mmHg and no history of antihypertensive treatment).

*Statistical analysis: Independent t-test. *p<0.05, **p<0.01 and ***p<0.001. Volumes were adjusted for intracranial volume (ICV).*

5 DISCUSSION

In this section, each study will be discussed separately. Previous research work is briefly described. Clinical implications are considered as well as strengths and limitations of the methods. At the end, future research directions are discussed.

5.1 STUDY I: STROKE AND DEMENTIA IN THE OLDEST OLD

There is limited research on the oldest old, although this is a population group increasing in numbers. It is estimated that there will be more than 21 million nonagenarians by 2050 in the world [174]. Our study showed that more than half (54.4%) of the participants developed dementia by 97-years of age [160].

It is well documented that stroke increases the risk for later development of dementia [128], and previous studies indicate less associations between dementia after stroke with increasing age. In the younger elderly group (≥60 years) with a history of stroke there is nine times increased risk for dementia [175], in 70- to 80-year-olds seven times [176], in 80-year-olds almost five times [176], and in 85-year-olds four times [177] increased risk. In the oldest old (97-year-olds), a history of stroke resulted in an almost two-fold risk for dementia. The decreased association between stroke and dementia with age may have several explanations.

First, we need to consider that participants in our study may have been exposed to a less severe stroke/TIA, as they survived. Outcome for a stroke/TIA in the very old is previously reported to be very poor [178, 179]. The differences between women and men are another important topic. We found that stroke/TIA was related to dementia in women, but not in men. In this study, there were more women than men; only 18.1% (107/591) of participants were men.

However, 72.8% of men invited to the study participated, and 63.3% of women participated. Only women had an association between stroke/TIA and dementia. It could be that men at this extreme old age, who are less common than women, may be a "surviving elite" with protective factors yielding high resistance to dementia. In a study on Swedish centenarians in 2009, there were 163 men and 712 women who celebrated their 100th birthday [180]. There were 3.7 females centenarians for every male centenarian in 2015 [181]. One other explanation for the non-significant association of stroke/TIA and dementia in men may be of a type II error. Of the 19 men with a stroke/TIA history in this study, seven had dementia – i.e., this under-power may result in a type II error.

We reported that living in an elderly care home was related to dementia and female sex but not to stroke/TIA. The reason why female sex was associated with living in an elderly care facility may simply be because more women than men had dementia (59.3% versus 32.7%), or men at this age, as we previously described, possess a high resistance to dementia. Dementia, and especially severe dementia, is one major reason for living in an elderly care facility [182].

There are some methodological considerations we need to address. One major limitation is the lack of computer tomography (CT) scans, a shortcoming that may have resulted in an underestimation of stroke, especially since silent strokes seem to increase with age [183]. However, there are also limitations with stroke diagnoses from CT scan; it is not always possible to determine the date of a stroke from a CT scan, which may lead to questions regarding its association with dementia development, and a TIA usually does not produce pathologic findings that a CT scan can detect [184, 185]. The validity of self-reports of diagnosed stroke or TIA could be questioned. However, our criteria were strict: only cases with a clear history of focal neurologic symptoms from stroke or TIA were diagnosed, although this strategy may underestimate the number of stroke/TIA. Other possible causes for underestimations could be that a key informant was missing in almost one-fourth (23.9%) of the cases. Another limitation is that the hospital discharge registers only captured a minority of all dementia cases in our study (16% had dementia according to the hospital register, compared to 54.4% in this study). Diagnoses of dementia in

the Hospital Discharge Register are often lacking in other countries as well [177].

Among the strengths in this study is the large sample size (n=591) of 97-year-olds in Gothenburg, Sweden. The response rate of 64.9% is satisfying in this age-group. In addition, participants were subjects to an extensive examination, and we used several information sources, including key informants. Future studies should investigate VaD and AD in the oldest old, especially VaD since some studies suggest that previous reported prevalence on VaD in the oldest old is overestimated [186, 187].

5.2 STUDY II: CSF MARKERS AND SURVIVAL

From previous studies, we know that mortality in participants suffering from AD is high [188, 189]. Clinical studies of patients with manifest AD have shown that those with highest levels of T-tau in CSF had increased mortality [85, 86]. We therefore aimed to investigate whether Alzheimer's pathological biomarkers – i.e., CSF Aβ42 and CSF T-tau – are associated with increased mortality also among non-demented individuals. A secondary aim was to examine whether levels of Aβ42 and T-tau in CSF was related to the development of dementia during a 15-year follow-up of 85-year-olds.

We reported that lower CSF Aβ42 and higher CSF T-tau at 85 years of age were associated with lower survival. Alzheimer's pathology biomarkers might interfere with brain controlled important body functions required for survival (e.g., blood pressure and cardiac function, fluid, and electrolyte control, including energy balance) [83, 84]. CSF Aβ42 is reported to exert neurotoxicity and neuronal cell death from different pathways (e.g., apoptosis, necrosis, and autophagy [190]) and axonal neurodegeneration is reflected as high T-tau in the CSF [191]. Brain atrophy on CT scan has previously been reported to be associated with higher mortality in persons without dementia [87] and the malfunction of the brain may affect essential body functions, resulting in less resistance to, for example, infections.

We suggest that in the very old (≥85 years) CSF Aβ42 relates to development of dementia only in a short-term perspective (three years) – i.e., not beyond the three years of follow-up. Thus, when evaluating CSF Aβ42 and CSF T-tau for AD, both age and the competing risks of death need to be considered. Preclinical signs of AD in CSF may not associate with development of dementia in very old, as a considerable proportion died within the next few years.

A major methodological consideration needs to be addressed within the limitations. We reported that the slope differences in CSF Aβ42 and CSF T-tau were not significantly different between participants with and without dementia (CSF Aβ42 p=0.11 and CSF T-tau p=0.31). However, this may be due to low statistical power, as there were only 65 participants in this study. Second, the response rate of 41.8%

accepting LP makes this study less representative for the general population. Because the LP was performed only once, we were not able to report changes in the CSF during follow-up. Finally, at the time the CSF analyses were performed, P-tau was not available; P-tau is a more specific biomarker for AD than T-tau [73]. Among the strengths of this study is that this sample was population-based, included participants without dementia, and had a long follow-up time with repeated examinations (analysing signs of cognitive decline or development of dementia) of all participants until their death.

In further research, we need to scrutinize the pathological mechanisms how Aβ42 damages the brain and this may ultimately result in better understanding of the increased mortality related to low CSF Aβ42 and high CSF T-tau.

5.3 STUDY III: BLOOD PRESSURE AND DEMENTIA

Previous studies have found that high BP is a risk factor for development of dementia [192, 193]. In individuals who developed dementia, BP levels decreased before dementia onset; in individuals with manifest dementia, BP levels were lower compared to individuals without dementia [137].

We report that BP levels were lower in 85-year-olds examined 2008–10 compared to 85-year-olds examined 1986–87. The lower BP levels may have multiple origins. One important explanation may be lowered threshold for initiating antihypertensive treatment in the very old [147]. In the 2008–10 examination, 61.3% were on antihypertensive treatment while in the 1986–87 examination, only 38.8% were on antihypertensive treatment. The use of antihypertensive treatment may not single-handed explain the decline in BP levels in the later examined cohort. Lifestyle changes were also associated with reduced BP levels: more physical exercise [194], less salt consumption [195], and healthier diets [196]. However, other risk factors increased in the later examined (2008-10) cohort such as overweight, diabetes, and life-time smoking [197].

Despite lower BP levels overall in the later examined cohort, individuals with dementia remained having lower BP-levels than individuals without dementia. This comparison between two cohorts suggests that the pathological processes in dementia affecting BP levels are independent of time trends. Lower BP levels in individuals with dementia may have several explanations. For example, individuals with dementia may have a more sedentary life. It may also be that brain regions involved in the BP-regulation may be affected by dementia pathology [198].

Although we found lower BP levels in later examined cohorts and further lower BP levels in participants with dementia, hypertension was still common. Almost half (46.5%) of the participants with dementia in the later cohort (2008–10) had a BP $\geq$140/90 mmHg; this is of clinical importance to notice.

The response rates of 60.5% in the 2008–10 examination and 64.2% in the 1986–87 examination suggest some limitations. We cannot exclude the possibility that non-attenders could differ from our participants. Furthermore, we used modern criteria for hypertension (i.e., ≥140/90 mmHg) in both cohorts. We were unable to adjust for different antihypertensive treatments and dosages. There could also be cases when antihypertensive drugs were prescribed for other reasons than lowering the BP. The strength of this study includes that the examinations used similar methods for both cohorts, whose members were born two decades apart.

In future studies, it will be important to scrutinize the pathophysiological processes in dementia that result in lower BP. In addition, investigate if early antihypertensive treatment could slow down the course and even prevent dementia. There are reports of a 55% incidence decline in VaD between the 1970s and 2010s [199]; this may be due to a lower threshold for start of antihypertensive treatment during the last decades [143], treatment higher up in age [147], and treatment of hypercholesterolemia [197]. However, this has to be considered in the context of increases in BMI and diabetes in the western world [197] and improving stroke survival [200], which may lead to an opposite effect on dementia incidence.

5.4 STUDY IV: HYPERTENSION AND ALZHEIMER BRAIN ATROPHY

Previous MRI studies have found that total brain volume is reduced in participants with hypertension [201, 202], especially midlife elevated BP was related to reduced total brain volume later in life [202]. We also know that hypertension is a risk factor for AD [193, 203], although the pathophysiological mechanisms responsible for this are not clear.

Therefore, we investigated the association between hypertension and brain atrophy in Alzheimer's specific brain regions. We found that hypertension, especially hypertension over time, was associated with reduced volume in Alzheimer's specific brain regions in 70-year-olds without dementia. Furthermore, we did not find any relation between hypertension and Alzheimer's associated CSF biomarkers (Aβ42, T-tau, and P-tau). This suggests that hypertension, unrelated to amyloid pathology, exerts neurodegeneration in Alzheimer's specific brain regions.

In line with our findings, there are reports on the association between high BP and hippocampus atrophy [204, 205] as well as temporal atrophy [206]. There are findings of hippocampus and temporal atrophy before clinical threshold of pathological CSF Aβ42 levels are reached [207], suggesting that hypertension also in the absence of Aβ pathology causes neurodegeneration in Alzheimer's specific brain regions. This is of importance in further research since according to the hypothesis of Jack *et al*. [78, 79] the first event in AD development is lowering of Aβ42 in CSF. Several years later neurodegeneration is found [78, 79] (see Figure 6). The mechanism for this neurodegeneration is not clear, CSF Aβ42 may cause brain atrophy by exerting neurotoxicity [190], but neurodegeneration is probably not a linear cascade of events followed by Aβ accumulation. Rather, there is a complex interaction of loops with feedback mechanisms [77]. These non-linear events may explain why individuals with history of hypertension had more deposition of Aβ plaques and NFTs than normotensive individuals [208, 209]. Furthermore, hypertension in cognitively normal participants was related to reduced glucose

metabolism in Alzheimer's specific brain regions on positron emission tomography (PET) [210, 211]. As hypertension and Aβ accumulation interact, we need to further investigate these mechanisms. Longitudinal studies reported that in individuals with hippocampus atrophy, 80% developed AD within four years [212], and atrophy in temporal regions was associated with progression toward clinical AD [76]. Hence, it is clinically important to treat and prevent hypertension to, if possible, avoid atrophy in Alzheimer's specific brain regions.

In this study, hypertension was not associated with CSF Aβ42, T-tau, or P-tau levels. It may be that our participants were too early in the disease course to exhibit a relationship with AD biomarkers in CSF. However, in this group we previously reported that almost half had some AD pathology in CSF [213].

We need to consider some methodological limitations. This was a cross-sectional study, the cause-effect relations are limited. Diagnosis of hypertension more than ten years before the study was self-reported, so there may be recall bias. In BP measurements, there is also a possible white coat effect, with elevated measurements only during the examination of the BP [214]. Antihypertensive treatment could be prescribed for other reasons than hypertension and different antihypertensive medications may have had different effects on lowering the BP or preserving Alzheimer's specific brain regions. Among the strengths is the population-based sample, with a comprehensive examination including MRI and CSF in participants of the same age. The effect of age on ICV is small but exists [169], therefore it was a strength that all participants were 70 years old. Future research should investigate whether participants in this study with atrophy in Alzheimer's specific brain regions will develop cognitive impairment and eventually AD.

6 CONCLUSION

Hypertension and AD biomarkers (e.g., Aβ42) probably potentiate each other, but this relationship needs further investigation. In this thesis, we reported that AD biomarkers were associated with mortality in older individuals. We further reported that dementia and risk factors for dementia such as stroke and hypertension are highly common in older individuals. Hypertension results in atrophy in Alzheimer's specific brain regions, and a BP $\geq$140/90 mmHg was found in more than half of 70-year-olds (54.8%) and 85-year-olds (56.9%).

7 FUTURE PERSPECTIVES

Future studies should continue to explore risk factors related to dementia since disease-modifying treatments for dementia are still lacking. Longitudinal data will be very helpful for the understanding of the association between risk factors and development of dementia. Participants in the 2014–16 examination (70-year-olds in study IV) are now 75 years old and re-examinations are currently ongoing (temporarily paused due to the Covid-19 pandemic). When data are available, we may be able to investigate whether participants with advanced cases of atrophy in Alzheimer's specific brain regions performed worse on cognitive tests or even developed AD.

Participants examined in 2014–16 with BP ≥140/90 were informed that they should see their general physician to have their BP levels re-evaluated and to discuss starting or adjusting current antihypertensive treatment. It will be of great interest to investigate whether those who received treatment and normalized their BP levels had less neurodegeneration of Alzheimer's specific brain regions.

Between 2029 and 2031, this cohort of 70-year-olds (examined 2014–16) will be 85 years old, and we plan to re-examine them again at that age. This data will be used to calculate prevalence of dementia and BP levels, enabling us to compare them with 85-year-olds examined 2008–10 (participants from study III). We will also examine several interesting research questions: Did overall BP levels further decrease? Does hypertension remain an usual condition? Does the prevalence of risk factors such as stroke, diabetes, and high BMI change?

Furthermore, it would be desirable if participants examined 2014–16 would consider another LP also at the age of 85 years. It would be of interest to analyse CSF data from participants who had a LP at 70 years of age and at 85 years of age and investigate the relation to cognitive decline and dementia development. This may further strengthen the amyloid cascade theory. I would further like to analyse hypertension in relation to cognitive decline and dementia development in participants with and without CSF pathology.

If we are able to follow 70-year-olds examined in 2014–16 with repeated cognitive tests, we will be able to evaluate the course of dementia and sub-types of dementia related to CSF markers. With advanced age, mortality will increase exponentially, and it would be of interest to re-evaluate if CSF biomarkers and new CSF biomarkers (including P-tau) are associated with survival or increased mortality (similar to study II). Although mortality is high with increasing age, a considerable proportion of participants in this cohort will reach 97 years of age. We will then be able to renew prevalence data on dementia and stroke/TIA. It would enable us to investigate whether this cohort has lower prevalence of dementia and stroke/TIA maybe as a result of antihypertensive treatment, reduced risk factors, and other cohort effects.

A huge advantage in epidemiological studies is that with extensive examination we are able to investigate several hypotheses. However, what we learned from this cohort may not be true in the following cohort. Thus, investigating new cohorts should never stop in order to bit-by-bit contribute to solve the puzzle of AD and VaD.

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APPENDIX