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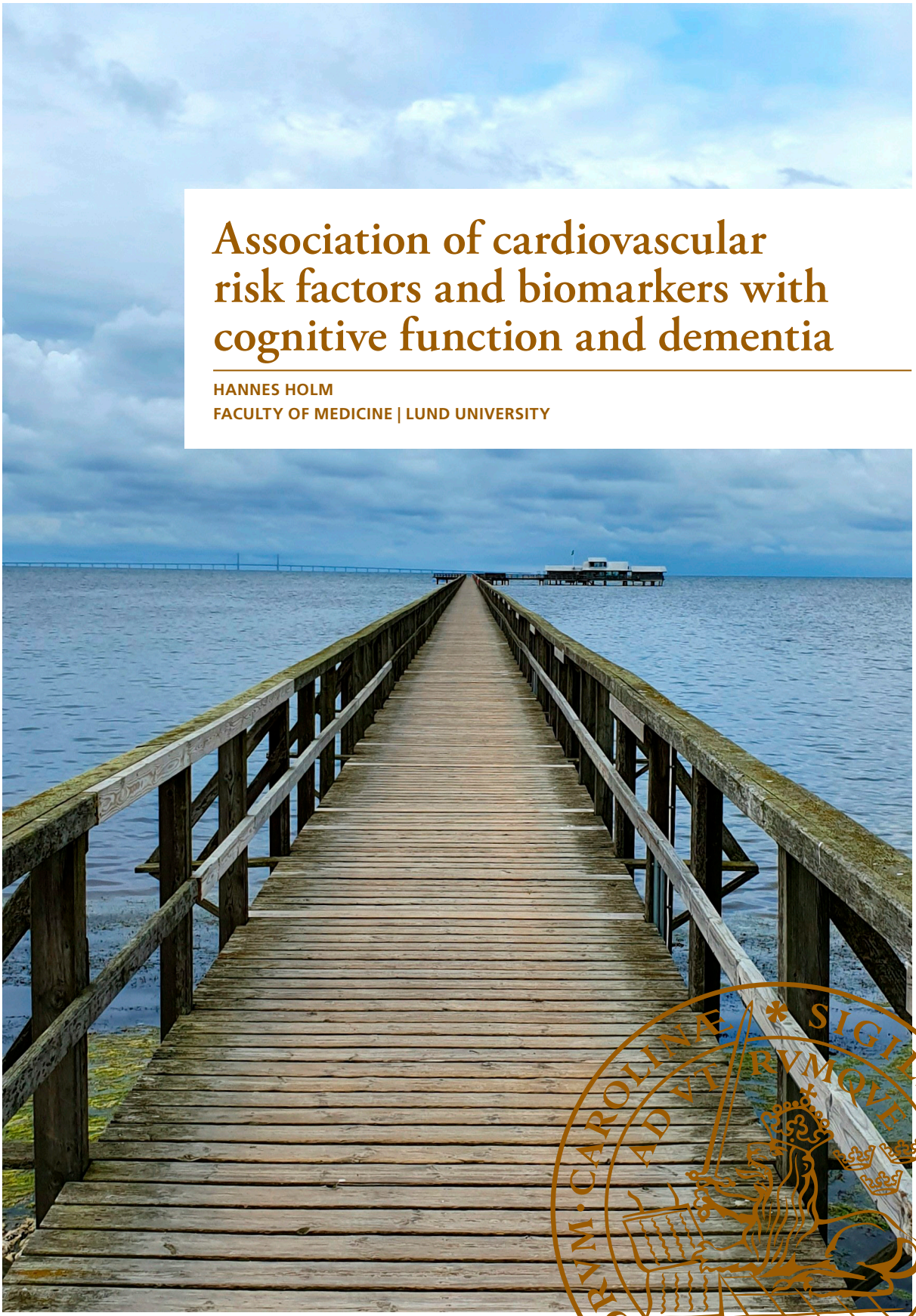

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Association of cardiovascular risk factors and biomarkers with cognitive function and dementia

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Abstract

The overall aim of this thesis was to investigate the relationship between specific cardiovascular risk factors (e.g. blood pressure, orthostatic hypotension and blood pressure lowering medication) and vasoactive biomarkers with risk of dementia development as well as evaluating the role of cognitive testing in the prediction of mortality and rehospitalization in a Swedish prospective heart failure patient cohort.

In **Paper I**, we sought to explore how resting and postural blood pressure (BP) changes relate to incident dementia over a long-term follow-up. We found that lower BP in advanced age, decline in BP between mid-life and advanced age and diastolic BP (DBP) decrease upon standing in mid-life predicted development of all-cause dementia. In addition, higher systolic BP (SBP) and DBP in mid-life conferred to increased risk of vascular dementia, but not Alzheimer and mixed dementia.

Since **Paper I** indicated that alterations in blood pressure were related to incident dementia, we aimed to investigate in **Paper II** whether blood pressure related biomarkers could predict incident dementia amongst community-dwelling older adults. We found that that elevated plasma concentration of mid-regional pro atrial natriuretic peptide (MR-proANP) predicted all-cause and vascular dementia while marked increase in C-terminal proendothelin-1 (CT-proET-1) contributed only to vascular dementia risk. Mid-regional pro adrenomedullin (MR-proADM) did not confer to dementia risk after adjustment for traditional risk factors.

In **Paper III**, a study examining the longitudinal association of circulating N-terminal prosomatostatin (NT-proSST) with incident dementia we showed that higher levels of NT-proSST were significantly associated with an increased risk of vascular dementia whereas no association was observed with Alzheimer, all-cause or mixed dementia.

In **Paper IV**, we sought to evaluate the longitudinal relationship between use of beta-blockers, as a class, and incident risk of all-cause dementia, vascular dementia, Alzheimer and mixed dementia. We observed that use of beta-blockers, as a class, was associated with increased longitudinal risk of vascular dementia in an elderly population, regardless of cardiovascular risk factors, prevalent or incident history of atrial fibrillation, stroke, coronary events and heart failure.

Finally, in **Paper V**, we studied the predictive role of four cognitive tests for mortality and rehospitalization in a Swedish prospective heart failure patient cohort. We showed that lower score on Montreal Cognitive Assessment (MoCA), lower score on Symbol digit modalities test (SDMT) and longer time duration of Trail making test A (TMT A) and A Quick Test of Cognitive speed (AQT) yielded significant associations with increased mortality. Rehospitalization risk was significantly associated with lower MoCA-score, lower SDMT-score and longer TMT A-time.

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“We need to change our minds about people whose minds have changed.”
Dr. Allen Power

Contents

Papers included in thesis

I. Hannes Holm, Katarina Nägga, Erik Nilsson, Olle Melander, Lennart Minthon, Erasmus Bachus, Artur Fedorowski, Martin Magnusson. *Longitudinal and postural changes of blood pressure predict dementia: the Malmö Preventive Project*. European Journal of Epidemiology. 2017 32:327–336

II. Hannes Holm, Katarina Nägga, Erik Nilsson, Fabrizio Ricci, Olle Melander, Oskar Hansson, Erasmus Bachus, Martin Magnusson*, Artur Fedorowski*. *Biomarkers of microvascular endothelial dysfunction predict incident dementia: a population-based prospective study.* Journal of Internal Medicine. 2017 282:94–101

III. Hannes Holm, Katarina Nägga, Erik Nilsson, Fabrizio Ricci, Eduardo Cinosi, Olle Melander, Oskar Hansson, Erasmus Bachus, Martin Magnusson*, Artur Fedorowski*. *N-Terminal Prosomatostatin and Risk of Vascular Dementia*. 2017 44:259-265

IV. Hannes Holm, Fabrizio Ricci, Gisueppe Di Martino, Erasmus Bachus, Erik Nilsson, Patrizia Ballerini, Olle Melander, Oskar Hansson, Katarina Nägga, Martin Magnusson, Artur Fedorowski. *Beta-Blocker Therapy and Risk of Vascular Dementia: a Population-Based Prospective Study.* Currently submitted to European Heart Journal - Cardiovascular Pharmacotherapy

V. Hannes Holm, Erasmus Bachus, Amra Jujic, Erik Nilsson, John Molvin, Lennart Minthon, Artur Fedorowski, Katarina Nägga*, Martin Magnusson*. *Cognitive test results predict mortality and post-discharge rehospitalization risk among Swedish heart failure patients.* Currently submitted to European Journal of Heart Failure

** Shared last authorship*

Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
Aβ	Beta-amyloid
AD	Alzheimer's disease
AHT	Antihypertensive treatment
ANP	Atrial natriuretic peptide
AQT	A quick cognitive test
BB	Beta blockers
BBB	Blood brain barrier
BMI	Body mass index
BP	Blood pressure
CBF	Cerebral blood flow
CCB	Calcium channel blockers
CT-proET-1	C-terminal proendothelin-1
CNS	Central nervous system
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiography
ESC	European society of cardiology
FTD	Frontotemporal dementia
HARVEST	HeARt and brain failure inVESTigation study

HF	Heart failure
ICD	International classification of diseases
LBD	Lewy body disorder
MCI	Mild cognitive impairment
MoCA	Montreal cognitive assessment
MPP	Malmö preventive project
MRI	Magnetic resonance imaging
MR-proADM	Mid-regional pro adrenomedullin
MR-proANP	Mid-regional pro atrial natriuretic peptide
NFT	Neurofibrillary tangles
NP	Natriuretic peptides
NT-proSST	N-terminal prosomatostatin
OH	Orthostatic hypotension
PET	Positron emission tomography
SBP	Systolic blood pressure
SDMT	Symbol digit modalities test
SNPR	Swedish national patient register
SVD	Small vessel disease
TMT	Trail making test
TTE	Transthoracic echocardiogram
VaD	Vascular dementia
VaMCI	Vascular-based mild cognitive impairment
VCI	Vascular cognitive impairment
WMH	White matter hyperintensities

Introduction

Age-related cognitive decline

According to the Oxford Concise Medical Dictionary, cognition can be defined as;

"a mental action or process of acquiring knowledge and understanding through thought, experience, and the senses." [1].

Since cognition encloses several areas of research, the definition is interpreted from different perspectives involving medicine, education, philosophy and computer science. From a medical point of view, cognition refers to the individual's ability to maintain normal cognitive functions including complex attention, executive function, learning and memory, language, perceptual-motor speed, or social cognition[2]. In order to live an independent life with capacity to deal with daily challenges, normal cognitive functions are essential. The main focus of this thesis involves approaches to find how different factors signaling vascular risk might affect the development of cognitive disorders such as dementia. In order to fully comprehend how cognitive disorders affect the human brain, it is therefore necessary to understand how cognitive abilities changes during the course of normal ageing.

Starting at an age of 20, several cognitive functions exhibit a linear course of decline[3] whereas in older ages, a more prominent reduction in cognitive functions appears, suggesting a curvilinear trend[4]. The cognitive domains most commonly affected by increasing age are the abilities to sustain normal attention, memory and executive functions[4, 5]. Compared to younger adults, older individuals appear to have more difficulties to divide or switch between tasks that require full attention[5], while ageing does not to the same extent affect the ability to maintain selective attention, i.e. the capacity to concentrate on the same task without being distracted by other stimuli[5]. Both working and long-term memory are declined by advancing age[6, 7]. In particular, the episodic memory which allows the individual to memorize personal experiences becomes diminished whilst the semantic memory is better preserved[8]. The age-related memory decline probably derives from inability to ignore irrelevant information and reduced processing speed which is imperative for tasks that require a timed response[9]. Despite that auditory accuracy and speech discrimination decline by older age[3], vocabulary and language abilities remain stable and may even improve[10]. Further, cross-sectional data from the Seattle Longitudinal Study suggests that the numerical ability improves by ageing[11].

Age-related cognitive decline might be attributed to structural and functional changes appearing in the central nervous system (CNS). By older age, the two main components of the brain, grey and white matter, become less voluminous, predominantly in the prefrontal areas[12]. The grey matter volume shows a linear trend of reduction until the age of 70[13]. Thereafter, the volume loss is accelerated, especially within the hippocampus area. In contrast, the white matter displays a U-shaped pattern of volume change with growing volume from early adulthood to middle age and thereafter a linear course of reduction[4]. These structural changes might explain the cognitive differences between older and younger individuals[14]. Furthermore, it has been shown that approximately 10 percent of neurons within the CNS undergo cell death during the course of normal ageing[15, 16]. However, cognitive decline is not solely explained by neuronal death, but also by a morphologic change within neurons such as decrease of the number of axons, dendrites and synapses[10, 17]. With advanced immunohistochemistry imaging techniques, continual decline in synaptic density has been observed during ageing and previous reports have proposed that onset of dementia occurs when approximately 40 % of neocortical synapses are lost[18].

Dementia and cognitive impairment

Dementia is defined as a clinical syndrome, associated with decline of cognitive abilities which negatively affects the individual's independence and ability to live a normal functional life. In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the term dementia has been replaced by the diagnosis of major neurocognitive disorder which is almost identical in terms of how to characterize the state of cognitive decline[19]. In contrast to previous versions, the manifestation of memory decline is no longer compulsory and diagnosis now only requires cognitive decline in one cognitive domain[20]. Detailed criteria of major neurocognitive disorder according to DSM-5 is listed in **Table 1**.

Table 1. Diagnostic criteria for major neurocognitive disorder according to DSM-5

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
C. The cognitive deficits do not occur exclusively in the context of a delirium.
D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Dementia represents one of the leading risk factors for overall mortality and disability among elderly individuals[21]. Despite that recent studies suggests that the incidence of dementia in western countries declines, it still constitutes a global health issue with increasing numbers of affected[22-25]. In 2015, the estimated number of individuals suffering from dementia worldwide was 47 million but due to large increase in life expectancy and absence of disease modifying treatment, the prevalence of dementia is expected to 131 million by the year 2050[26]. In 2018, the global cost of dementia care was estimated to exceed one trillion dollars. In a study from the United Kingdom, the health and social care costs for dementia surpassed that of cancer and heart disease combined[26, 27].

Several conditions have been outlined as underlying pathologic disorders responsible for dementia onset and progress. Of these, Alzheimer disease (AD) represents the most common cause of dementia which in this thesis will be referred to as AD dementia[28]. Next to AD dementia, vascular dementia (VaD) is considered as the second most common dementia subtype followed by dementia with Lewy bodies (LBD) and frontotemporal dementia (FTD) [29-31]. The prevalence of these separate subclasses of dementia varies considerably. Increasing evidence indicates that vascular pathology is highly prevalent in patients with AD dementia and that patients with VaD exhibit pathophysiologic hallmarks of AD[32]. This overlap between the two conditions is entitled mixed dementia and is currently recognized as one of the major dementia subclasses for older individuals[33].

The clinical diagnosis of dementia is often challenging as impairment of cognitive functions might be initiated by a wide range of somatic diseases including vitamin deficiency, infections and heart failure[34]. In contrast to dementia, the cognitive deficits these conditions cause are reversible. Mild cognitive impairment (MCI) can be described as a transit zone between normal ageing and dementia[35]. However, MCI does not limit the independency in daily activities and is practically equal to the condition of minor neurocognitive disorder presented in DSM-5[19]. The concept of MCI has gained considerable attention as 5 to 10% of individuals with MCI every year will emerge to meet the diagnostic criteria for dementia[36].

Vascular cognitive impairment

In the DSM-5 diagnostic criteria, the term VaD has been replaced by major vascular neurocognitive disorder which is regarded as “a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain”, see **Table 2**[19, 37]. Today, the use of vascular cognitive impairment (VCI) is considered as a far more appropriate concept than VaD since VCI includes all levels of cognitive decline due to cerebrovascular disease, ranging from vascular-based mild cognitive impairment (VaMCI) to VaD where independence in everyday activities is affected[37]. In contrast to other VaD diagnostic criteria, including the International Classification of Diseases, 10th

edition (ICD-10)[38] and National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS–AIREN)[39], the DSM-5 criteria does not require focal signs of neurologic deficits. Due to the diverse pathological features of VaD and the inconsistency between the severity of symptoms in relation to infarct volume and number, no neuropathological criteria exists [37, 40].

Table 2. Diagnostic criteria for Major Vascular Neurocognitive Disorder according to DSM-5

A. The criteria are met for major neurocognitive disorder.
B. The clinical features are consistent with a vascular etiology, as suggested by either of the following:
1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.
2. Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function
C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits
D. The symptoms are not better explained by another brain disease or systemic disorder. Probable vascular neurocognitive disorder is diagnosed if one of the following is present; otherwise possible vascular neurocognitive disorder should be diagnosed:
1. Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimagingsupported).
2. The neurocognitive syndrome is temporally related to one or more documented cerebrovascular events.
3. Both clinical and genetic (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present.
Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.

As mentioned above, VaD is the second most common type of dementia, accounting for at least 15 to 30 % of all cases[28, 40, 41], depending on variations in sampling methods, country demographics and diagnostic criteria. The most prominent cognitive deficits are executive dysfunction and reduced psychomotor speed whereas memory is better preserved compared to AD dementia [42-44]. The underlying pathological mechanisms are heterogenous involving large and small vessel sclerosis, amyloid angiopathy and other vasculopathies[41]. In the past decades, the presence of multiple large and small infarcts was regarded as the main etiologic factor in development of VaD[45]. Nowadays, small vessel disease (SVD), historically known as Binswanger disease is considered as the most common cause of VCI[46, 47]. SVD evolves from thickening of the capillary basement membrane initiating endothelial leakage and microthrombi, systemic arteriolar dysfunction and local hypoperfusion[47-49]. These changes can be displayed as white matter hyperintensities (WMH), lacunar infarcts, microbleeds and visible perivascular spaces on magnetic resonance imaging (MRI) of the brain[41, 47]. The pathological structural changes typically appear in subcortical areas and the pattern of cognitive deficits depends on which brain region is affected. Typically, both large and small vessel disease coexist and are implicated in cortical and subcortical manifestations[41]. Recent studies have shown that cerebrovascular manifestations

associated with SVD cause impaired communication between cortical and subcortical brain areas[50, 51]. The symptoms of SVD are initially often subtle and in many cases not recognizable for the patient or clinicians[47].

Alzheimer dementia

Alzheimer's disease is the most common cause of dementia with a prevalence of 5 to 6 % in individuals above the age of 65, and up to 30 % in the very old over the age of 85[52]. Several criteria guidelines for AD diagnosis have been outlined, including criteria from the National Institute of Aging (NIA)[53], the International Working Group (IWG-2)[54] and DSM-5[19]. These guidelines recognize that AD enfolds a broad spectrum of disease progress. According to DSM-5, cognitive decline due to AD is defined as a major neurocognitive disorder which includes all levels of cognitive severity, from preclinical AD dementia to fully developed AD dementia, see **Table 3**. Progressive memory decline followed by topographical disorientation and reduced executive ability usually appears several years before the final diagnosis of AD dementia[55].

Table 3. Diagnostic criteria for Major Neurocognitive Disorder Due to Alzheimer's Disease according to DSM-5

A. The criteria are met for major neurocognitive disorder.
B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).
C. Criteria are met for either probable or possible Alzheimer`s disease as follows: Probable Alzheimer´s disease is diagnosed if either of the following is present; otherwise, possible Alzheimer`s disease should be diagnosed:
1. Evidence of a causative Alzheimer`s disease genetic mutation from family history or genetic testing.
2. All three of the following are present:
a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).
b. Steadily progressive, gradual decline in cognition, without extended plateaus.
c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systematic disease or condition likely contributing to cognitive decline).

The gradual development of cognitive decline is marked by a continuing cerebral accumulation of beta-amyloid (Aβ) neuritic plaques (also known as senile plaques) and tau-containing neurofibrillary tangles (NFTs). These two cardinal hallmarks of AD cause progressive neurodegeneration with the downstream consequence of brain atrophy especially in the temporal lobe[56]. Mostly, AD dementia occurs sporadically but gene testing now offers the possibility to find autosomal dominant etiology including mutations in the amyloid precursor protein (APP), presenilin 1 and 2 (PSEN1, PSEN2)[57]. The most well-known risk gene for late-onset AD is ApoE which encodes Apolipoprotein E involved in clearance of Aβ. ApoE has 3 variants; ε2, ε3 and ε4 where the latter (ApoE4) is the single biggest risk for AD.

[58]. Approximately 70 % of AD risk is driven by genetic factors[56]. As the pathological changes of AD typically develops several years before clinical symptoms appear, a broad spectrum of diagnostic tools has been evolved to allow earlier diagnosis[59]. The pathological changes of AD can be detected in cerebrospinal fluid (CSF) where alteration of biomarkers such as decreased levels of Aβ and elevated levels of phosphorylated tau protein (p-tau) are observed[60]. The question what triggers the accumulation of Aβ and tau in the brain is today still unanswered, but several reports suggest that the onset of sporadic AD dementia is influenced by several causes including environmental and genetic factors[61].

Mixed dementia

According to DSM-5, mixed dementia is defined as a major neurocognitive disorder due to multiple etiologies[19]. Mixed dementia commonly describes the co-existence of neurodegenerative and cerebrovascular diseases whom are correspondingly contributing to clinical symptoms. Hence, the diagnosis of mixed dementia should be applied when a neurodegenerative disorder such as AD is present together with VaD. These separate entities might independently account for the impairment in cognitive function or potentiate the detrimental effect of one another. However, there is a lack of evidence whether this association is coincidental and cumulative or casual and synergistic. It has been increasingly recognized that conditions associated with CVD such as diabetes, hypertension and arteriosclerosis contribute to AD pathology progress[62, 63]. To illustrate this, participants in the Rotterdam population cohort with severe arteriosclerosis had three-fold increased odds for AD dementia (95% CI 1.5–6.0) compared to vascular healthy individuals[64]. Additionally, brain autopsy of elderly individuals free from dementia has revealed co-existence of cerebrovascular disease and AD, proposing a composite route of subclinical disease[65, 66]. Cerebral amyloid angiopathy (i.e. deposition of Aβ around cerebral vessels) have been shown as an important marker for AD but also for microinfarction, microhemorrhage seen in VCI[37]. As cerebrovascular pathology increases exponentially with increasing age, mixed dementia is particularly found in individuals older than 85 years[67]. Due to the complex heterogeneous etiology and absence of consensus regarding diagnostic criteria, mixed dementia has not been sufficiently studied. Since the co-existence of cerebrovascular disease and AD has shown to be common in many elderly individuals with dementia, there is a growing interest of finding biomarkers with potential to distinguish between the two entities. Therefore, one of the purposes in this thesis has been to investigate whether certain biomarkers are attributable to certain dementia subtypes.

Risk factors

Risk factor definition

In epidemiology, the probability that an event will occur can be defined as risk. The presence of risk factors enhances the probability that a particular outcome will appear[68]. According to the Oxford Medical Dictionary, a risk factor is defined as;

> ” an attribute, such as a habit (e.g. cigarette smoking) or exposure to some environmental hazard, that leads the individual concerned to have a greater likelihood of developing an illness. The relationship is one of probability and as such can be distinguished from a causal agent.”[1]

The risk factor can remain constant or variate during the life course. Variable risk factors such as blood pressure or plasma level of fatty acids are often modifiable which allows them to be treated. Further, a risk factor may be causative, expressing the underlying biology of a certain disease but also solely predictive, identifying individuals at higher risk[69]. Considering this, a risk factor should not be mistaken for a risk marker which describes an attribute or exposure that is associated with increased probability of disease, but is not necessarily a causal factor[70]. If the risk factor of interest is predictive but not causative, changing or treating the factor might not affect the expression of the disease. For example, lowering blood pressure in individuals with hypertension has evolved in lower incidence of cardiovascular disease in this group. However, CVD as well as dementia is based on a multifactorial ethologic background, implying that not all hypertensive individuals will develop CVD and not all of those with CVD are hypertensive. Therefore, an ideal risk factor is not only causative but also independent with high sensitivity and specificity of the outcome[69]. In addition, the risk factor should also have a high external validity, not depending on the characteristics of the population. To be used in clinical practice, the risk factor should also be easily assessable.

Risk factors of dementia

Several risk factors of cognitive decline and dementia have been presented in large population cohort studies[71, 72]. As mentioned above, the pathophysiological etiology of dementia is multifactorial. A risk factor of dementia might therefore exert the negative influence on its own or interact with other factors, potentiating the detrimental cognitive effect[73, 74]. Hence, it is difficult to conclude whether the risk is mediated through one or several co-existing risk factors. Additionally, risk factors emerge at different time points during the lifespan which adds to the complexity on how to estimate the effect of risk[75]. Another important aspect when interpreting studies that investigate the relationship between risk factors and cognitive decline, is the lack of causality. How the risk factor exerts its negative effects is often left to speculations. Furthermore, the time between risk factor

identification and dementia diagnosis is rather short in several studies. Hence, dementia progress might influence the risk factor by ways of reversed causation. For example, hypotension has been reported as an independent risk factor for dementia. Conversely, dementia progress often involves brain areas responsible for blood pressure regulation[76].

The most significant risk factors of dementia are unmodifiable including advancing age, genetic susceptibility and familiar history[71]. Since no disease-modifying treatment or cure for dementia exists, it becomes exceedingly important to detect modifiable risk factors for the development of cognitive decline and dementia. As mentioned above, growing evidence demonstrates that dementia incidence is declining in western populations[22-24]. This reduction is believed to be the entailed effect of improved educational level and cardiovascular health[25]. It has been suggested that public interventions targeting cardiovascular risk factors might serve as a protective approach to reduce the risk of dementia development[77, 78]. Therefore, numerous interventional trials have been conducted to find potential beneficial effects on cognition by removing modifiable risk factors. However, outcomes have been inconsistent and difficult to draw any conclusions from[79-81]. Approximately one third of all dementia cases due to AD are possibly attributed to modifiable risk factors including diabetes mellitus, midlife hypertension and obesity, physical inactivity, depression, smoking, and low educational attainment[82]. In several cases, risk factor exposure appears long before the onset of dementia symptoms, which makes it even more important to detect high-risk individuals at an early time point[83, 84]. As mentioned above, cognitive decline is a part of the normal ageing process and should not necessarily be considered as a marker of dementia progression[3]. Several studies do not restrict normal cognitive decline as its own process but instead as a marker of dementia. Cardiovascular risk factors do not only exert higher risk of VaD but also increase the risk of AD dementia[61, 85]. Consequently, there is a lack of knowledge regarding which risk factor that is attributable to certain dementia subtypes. In this regard, one of the purposes of the thesis has been to investigate how different levels of blood pressure in a population cohort might influence the risk of different dementia subclasses.

Resting blood pressure

Resting blood pressure has been closely studied in relation to cognitive decline and dementia[86-88]. Since BP regulation is an important factor in maintenance of cerebral circulation, both hyper, - and hypotension have been associated with impairment of brain structure and function. Additionally, BP changes upon orthostatic challenge has been linked to cognitive decline and dementia[89, 90].

Hypertension represents one of the primary reasons of premature mortality [91]. In 2015, the global prevalence of hypertension was estimated at 35 to 45 %,

irrespective of income status[92]. In individuals suffering from dementia, a wide range of hypertension prevalence has been reported from 35 to 84%[93].

In autopsy studies of older individuals, brain AD pathology with neurofibrillary tangles and neuritic Aβ plaques have been closely linked to hypertension[94-96]. By using positron emission tomography (PET), higher amounts of Aβ in the brain have been observed in individuals with high SBP and DBP[97, 98]. Prospective longitudinal studies have described hypertension in mid-life as one of the main CVD risk factors for late-life dementia development including both VaD and AD dementia[84, 99-101]. The association between increasing SBP in mid-life and future decline in cognitive domains seems to be linear whilst the longitudinal relation between mid-life DBP and cognitive impairment appears to be U-shaped[102, 103]. Although, antihypertensive treatment during mid-life has not been followed by reduced risk of late-life dementia, lowering blood pressure has been associated with beneficial effects on cognitive functions[104, 105].

In older age, only the most extreme values of BP elevation (SBP >180mm Hg) have proven to increase the risk of dementia outcome[84]. On the contrary, older individuals with dementia exhibit lower BP levels compared to healthy age-matched persons. The reduced BP has been observed within the years before the onset of dementia[84, 106]. Therefore, reversed causation has been suggested where brain lesions caused by dementia progress result in hypotension[76]. In a newly published report including 1,440 individuals in the Framingham Offspring study, a steep reduction of systolic blood pressure in midlife to older age doubles the risk of AD dementia and dementia overall[107]. There is an ongoing debate whether lowering the blood pressure might have positive or negative effects on cognition. In a large randomized clinical trial including 8, 563 participants with a mean age of 68 years, no beneficial outcome on dementia incidence was observed by treating the blood pressure to 120 compared to 140 mmHg[104]. Peng J et al. described cognitive impairment and faster progress of WMH for elderly patients (>80 years) who were treated to systolic BP beneath 140 mmHg[108]. These findings are intriguing since antihypertensive treatment later in life has been associated with beneficial effects on cardiovascular outcomes. However, the question has been raised which BP threshold should be used in order to avoid concomitant cognitive decline and dementia.

Orthostatic hypotension and orthostatic intolerance

Orthostatic hypotension (OH), is defined by a decrease in SBP of ≥20 mmHg and/or DBP decrease of ≥10 mmHg within three minutes of standing and is a common condition among older individuals[109]. Clinical signs of OH are lightheadedness, blurred vision, weakness and nausea. However, many patients do not exhibit any symptoms and are therefore unaware of the condition. OH has been associated with increased risk of cardiovascular diseases and mortality in large population

cohorts[110, 111]. As mentioned above, CVD constitutes a major risk factor for dementia, not only for VaD but also for AD dementia[61, 85]. Hence, there is a growing interest to explore whether OH might increase the risk of cognitive decline and dementia. Cross-sectional studies have shown that dementia is common among individuals with OH, compared to healthy age-matched subjects[112]. Wolters et al. reported a longitudinal association between OH with increased risk of dementia, a relationship mainly driven by insufficient compensatory increase in heart rate[90]. Also, symptoms of orthostatic intolerance in personal history has been associated with mild cognitive decline[113]. The drop of BP in reaction to orthostatic challenge might induce cerebral hypoperfusion and if compensatory mechanisms such as increased heart frequency and proper response by cerebral autoregulation fails to maintain cerebral blood flow, cerebral ischemia might follow[114, 115]. As many patients with OH lack clinical signs of underlying disorder, recurrent episodes of cerebral ischemia might go unnoticed but in the long term contribute to the risk of dementia. To date, only two studies have been able to demonstrate a longitudinal association between OH and dementia whereas one of these did not adjust for cardiovascular risk factors aside from hypertension[90, 113]. At the time when **Paper 1** was conducted, no prior studies had investigated the relation between OH and incident dementia.

Diabetes

Several observational and longitudinal studies have depicted diabetes as a significant risk factor for cognitive decline and dementia[116, 117]. Furthermore, the presence of diabetes increases the risk of conversion from cognitive impairment into dementia[118]. The mechanism underlying this relationship is probably multifactorial since diabetes can be associated with multiple cardiovascular risk factors, including obesity, insulin resistance, atherogenic dyslipidemia, hypertension, and proinflammatory states[119-122]. Additionally, diabetes increases the risk of ischemic stroke and SVD seen in VaD[123]. Diabetes has also been implicated in the risk of AD which is likely due to coexistence with several other cardiovascular risk factors[124].

Heart failure

According to the European Society of Cardiology (ESC)[125], heart failure (HF) is defined as;

"a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress"

Based on left ventricular ejection fraction (EF), HF is categorized into three subclasses, including HF with reduced EF (HFrEF; EF≤40%), HF with mid-range EF (HFmrEF; EF 40-50%) and HF with preserved EF (HFpEF; EF≥50%)[125]. Structural and functional cardiac changes are often present before clinical signs of HF appear. Since the occurrence of these changes are associated with increased mortality and co-morbidity, it is important to identify them at an early stage[126]. The diagnosis of HF is based on the patient's prior clinical history, physical examination, electrocardiography (ECG), measurement of natriuretic peptides and transthoracic echocardiogram (TTE)[125]. The etiology of HF is multifactorial and varies within different world regions. Most common pathophysiological causes are ischemic heart disease, abnormal loading conditions and arrhythmias[125]. Despite that treatment of HF has improved over recent decades, the mortality is still high with a 5-year survival rate of 45%, depending on the severity[127]. Every year HF causes more deaths compared to most malignant tumors[128] and is one of the most frequent reason for hospital admission among elderly[129, 130]. Additionally, the cost of HF treatment is considerably high[131].

Heart failure, cognitive decline and dementia

It has been increasingly recognized that patients who are hospitalized for HF show signs of cognitive disabilities in executive functions, memory, speech and mental processing speed[132-135]. Considering these observations, the term "cardiogenic dementia" was introduced in the 1970's to describe the relationship between HF and cognitive impairment[136]. Since then, several cross-sectional studies have been performed with the aim to report the prevalence of cognitive decline in HF, see **Table 4**. The results have been inconclusive with a wide range of cognitive decline prevalence, ranging from 25 to 75 % in different HF populations[137]. Despite being common comorbidities, cognitive impairment in HF is frequently not documented by physicians and clinical guidelines on how to address cognitive decline in HF are lacking or largely tentative[138, 139].

Table 4. Reported prevalence of cognitive decline in heart failure patients [140]

Author (year)	Study type	Setting	N	Prevalence of CD (%)	Prevalence of mild CD (%)	CD test used
Zuccala et al. (1997)	Cross-sectional	Mild-moderate CHF	57	53	NA	MMSE
Debette et al. (2007)	Prospective	Hospitalization for AHF	83	61	30	MMSE
Gure et al. (2012)	Cross-sectional	Community (USA)	6,189	39	24	Telephone interview for cognitive status (patterned MMSE)
Hajduk et al. (2013)	Prospective	Hospitalization for AHF	577	79	NA	Specific protocol*
Dodson et al. (2013)	Prospective	Hospitalization for AHF	282	47	25	MMSE dur to AHF
Levin et al. (2014)	Prospective	Hospitalization for AHF	744	80	32	Specific protocol*
Hyunh et al. (2016)	Longitudinal	Hospitalization for AHF	565	45	NA	MoCA

*Specific bedside protocol: test of immediate and delayed memory (subscale of MoCA), processing speed (Digit Symbol Substitution Test, DSST) and executive function (Controlled Oral Word Association Test (COWA) for verbal fluency). AHF = acute heart failure; CHF = chronic heart failure, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment.

Among patients with HF and concomitant cognitive decline, a twofold increase in 30-day mortality and rehospitalization has been observed[141], as well as an almost fivefold increased risk of 1-year mortality[142]. The risk of rehospitalization among HF patients is highest in those with unrecognized cognitive decline[139]. Additionally, the risk of progression of cognitive decline to dementia has been reported to be higher in HF patients compared to healthy aged-matched individuals[143]. Cognitive impairment likely contributes to the inability to manage complex medical regimens and recognize worsening symptoms[144]. For example, individuals with HF are taught by medical providers to monitor daily weights and breathing status which require intact memory and executive functions.

With an increasing population age and improved survival of acute coronary syndromes, the number of patients suffering from HF will keep rising and therefore it is important for physicians to detect patients with HF at risk to develop impaired cognitive function. By detecting these patients at an earlier stage and optimizing their medical treatment may not only prevent the progression of HF but also the development of impaired cognitive function. Currently, there is a lack of knowledge in regard to which cognitive domains that are affected in HF patients. To address these questions, this thesis enfolds a paper in which several cognitive tests have been used to examine which cognitive functions that are most affected in HF patients. Additionally, cognitive test results are longitudinally associated with the risk of all-cause mortality and rehospitalization among HF patients.

Antihypertensive treatment

It has been concluded in large meta-analyses and systematic reviews that antihypertensive treatment (AHT) reduces the risk of CVD, renal disease, stroke and overall mortality[145, 146]. Traditionally, the indication for AHT has been recommended when systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg[147]. In certain patient groups including individuals with diabetes or renal disease, a lower BP limit has been advocated. In elderly individuals, higher BP targets have been applied to avoid falls and risk of fractures. Currently, the trend towards lower BP thresholds now enfolds even older individuals where the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the detection, prevention, management and treatment of high blood pressure states that "Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher"[148]. Lower BP thresholds for elderly individuals (aged over 80 years) was also recommended in ESC/ESH 2018 guidelines for the management of arterial hypertension[147]. These recommendations referred to findings in the *SPRINT trial* published in 2017, where treatment of the SBP to less than 120 mm Hg decreased the risk of fatal and nonfatal major cardiovascular events and death from any cause compared to a SBP target less than 140 mm Hg[149]. Nevertheless, optimal blood pressure, particularly in elderly individuals, remains a topic of discussion since the *SPRINT trial* also showed that intensive BP treatment significantly increased the risk of some adverse events including hypotension, syncope, electrolyte abnormalities, and acute kidney injury. With advancing age, the elasticity of blood vessels is reduced which leads to a decline of the autoregulatory capabilities of cerebral arteries[150]. The diminished autoregulatory capacity may result in cerebral ischemia when blood pressure drops below a critical threshold for maintaining adequate cerebral perfusion[151]. Transient episodes of cerebral ischemia have been suggested to contribute in cognitive impairment and dementia progress[152]. BP-lowering drugs might therefore have the adverse effect on cognition by decline in cerebral perfusion. In order to explore whether AHT is longitudinally associated with dementia, this thesis enfolds a paper with the aim to shed light upon this issue.

The impact of antihypertensive treatment on cognitive impairment and dementia

Since no curative therapy for dementia exists, it is essential to determine which medicines that might have beneficial effects on dementia risk factors. As mentioned above, chronic hypertension constitutes a major risk factor for both AD and VaD development[86, 88]. These findings emphasize the potential role of AHT to reduce the risk of cognitive decline and dementia. However, the literature regarding the potential beneficial role of AHT on cognitive function is conflicting[88]. Several trials have investigated the cross-sectional association between AHT and cognitive

decline whereas most have been able to show that AHT exerts protective cognitive effects. Furthermore, longitudinal studies have shown promising results suggesting an inverse relationship between AHT and incident all-cause and AD dementia. A large meta-analysis of 12 studies concluded that AHT reduced the risk of cognitive impairment and dementia by 9 % [153]. However, many trials have failed to confirm the potential beneficial role of AHT for cognition whereas the introduction of AHT has in contrary been shown to diminish cognitive function[154-156].

Several methodological factors have been suggested to explain the lack of association. For example, longitudinal studies are often limited by a lack of precision regarding the duration of treatment. Usage of antihypertensive agents are generally recorded at admission or discharge from hospital. Therefore, alteration in dose of treatment or termination of treatment during follow-up is commonly not documented[157]. Considering that AHT in mid-life has shown to exert the most beneficial effects on cognition[84, 158], introducing AHT in older age might not be as effective, **Table 5**. Studies with a high proportion of elderly individuals with hypertension might also be exposed to selection bias as elderly with no previous medical history of vascular events may not be representative. Another methodological issue in trials comparing placebo from active treatment is potential crossover between the groups. As mentioned above, trials are commonly using different cognitive tests to assess cognitive function. For example, participants in the Hypertension in the very elderly trial (HYVET) only performed the MMSE test which does not comprehend executive functions which are commonly impaired in VCI[154]. Consequently, individuals with high cardiovascular burden might be missed. Another important aspect to consider when interpreting studies that focus on AHT and cognitive impairment is a potential class effect of AHT. Subclasses of AHT including *Calcium Channel Blockers* (*CCB*), *Renin Angiotensin Aldosterone Inhibitors (RAAS), Angiotensin-AT1-receptor-blockers* (*ARB*) have all been associated with cognitive protective abilities[88]. To explain the beneficial effect of these AHT subclasses, several indirect mechanistic pathways have been proposed, but also local effects within the brain[157]. Treatment with lipophilic CCBs with the capacity to cross the blood brain barrier (BBB) have been reported to increase cognitive function in individuals with MCI[159]. The cognitive improvement was suggested as a result of increased cerebral blood flow observed in the same study participants.

Table 5. Population-based longitudinal studies of antihypertensive medication use in relation to dementia [84].

	Study description	Outcomes	Medications	Covariates*	Main results
Lindsay et al. 2002	A Canadian national sample of 3238 people (58% women) age≥65 years, follow-up 5 years	AD; DSM-IV	Antihypertensive agents	,,	RR 0,91 (95% CI 0,64-1,30)
Morris et al. 2001	A random sample of 634 people (63% women) from East Boston age≥65 years, follow-up 4 years	AD; NINCDS-ADRDA	Diuretics and β-blockers	,,	No association
Qiu et al. 2003	1270 people (75% women) from dementia-free community age≥75 years, median follow-up 5 years	Dementia, AD; DSM-III-R	Antihypertensive drugs	BP, MMSE score, vascular disorders	Dementia: RR 0,8 (0,6-1,0); similar for AD
in't Veld et al. 2001	A community cohort of 6416 non-demented people (59% women) in Rotterdam suburb age≥55 years, mean follow-up 2,2 years	Dementia, DSM-III-R; AD, NINCDS-ADRDA; VaD, NINDS-AIREN	Antihypertensive drugs	BMI, MMSE, stroke, atherosclerosis, BP, diabetes, smoking	Decreased risk of dementia and VaD, but not AD
Yasar et al. 2005	1092 dementia-free community volunteers (37% women) age≥60 years, followed up to 19 years	AD; NINCDS-ADRDA	DHP-CCB	BP, smoking, heart disease	RR 0,30 (95% CI 0,07-1,25)

*Demographic variables (ie, age, sex, education) were included as covariates in all studies. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edn; RR=risk ratio; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; BP=blood pressure; NINDS-AIREN=National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; BMI=body mass index; DHP-CCB=dihydropyridine type calcium channel blockers; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3rd edn (revised).

Beta blockers, cognitive decline and dementia

Beta blockers or beta-receptor antagonist were initially introduced in the 1960's for treatment of angina pectoris[160]. Beta blockers are today recommended as first line treatment for hypertension, heart failure and certain arrhythmias and have been

associated with beneficial effects on both short- and long-term survival after myocardial infarction[161]. By binding to adrenergic receptors (ADRs) and by that inhibiting central and peripheral effects of noradrenaline (NA) and adrenaline (AD), beta blockers provide a negative chronotropic and inotropic effect resulting in decreasing blood pressure, heart frequency and cardiac output[162]. The use of beta blockers has not been without compelling indications since other drugs for hypertension have proved to be more effective in reducing the incidence of stroke[163], and the composite measure of cardiovascular outcomes including stroke, myocardial infarction, and death[164].

The impact of beta blockade treatment on cognitive function has so far provided contradictory conclusions, as beta blockade has both been shown to preserve cognitive function and to reduce it[165-167]. To illustrate this, attenuated memory ability has been observed in both rodents and humans treated with the selective B_1-ADR antagonist propranolol, whereas infusion of an B_1-ADR agonist led to memory enhancement[168]. The longitudinal association between treatment with beta blockade and incident dementia has just recently been studied in a German cohort including elderly persons followed in general practices[167]. In this thesis, we sought to access the role of beta blockade treatment in regard to risk of dementia development.

Biomarkers for cognitive decline and dementia

Early and correct diagnosis of dementia disorders may contribute to identify individuals at high risk and for these subjects induce preventive therapy before dementia symptoms appear. The clinical diagnosis of dementia is often challenging as the diverse neuropathological patterns and symptoms of certain dementia subtypes co-exists[169]. The diagnostic accuracy of AD dementia has been reported to be wrong in 20 percent of cases[170]. In VaD, this number is probably higher, particular in elderly individuals where multiple pathology is common. In order to aid the diagnosis of both dementia and prodromal stages of dementia, the measurement of plasma derived biomarkers has gained much interest in clinical studies. According to the Oxford Medical Dictionary a biomarker may be defined as;

"a naturally occurring characteristic that reflects underlying normal physiological or pathologic processes[1]."

It may also mark the biological responses to a therapeutic intervention or procedure. Biomarkers can be of different types, including molecules in body tissues or fluids, performance on diagnostic tests or imaging measurements. For example, in AD dementia, the presence of cerebral Aβ plaques is reflected by biomarkers including CSF $A\beta_{42}$ or Aβ amyloid on imaging technologies including Positron Emission

Tomography (PET). The entailed effects of neurodegeneration and synaptic dysfunction can be observed with volumetric Magnetic Resonance Imaging (vMRI) and Fludeoxyglucose (FDG) PET respectively[55].

The primary purposes of biomarker assessment in dementia is to detect the presence of neuropathology, to identify individuals at higher risk and to define the stages of the disease. Additionally, biomarkers might also be a part of creating risk score tools such as the CAIDE Dementia Risk Score with documented ability to estimate the risk of dementia in a 20-year perspective[171]. The ideal biomarker has a high sensitivity and specificity in combination with high negative and positive predictive value for the endpoint of interest[172]. Furthermore, the biomarker should be stable over time, be reproducible and easily available[173]. Optimally, a biomarker should also reflect other diagnostic or predictive measurements for a certain disease.

When interpreting the diagnostic and predictive value of biomarkers, one must be aware that biomarkers might have different degrees of specificity and sensitivity depending on the stage of the disease[174]. Another important aspect regarding the utility of biomarkers is the age dependency. As for AD dementia, the diagnostic accuracy of CSF biomarkers declines by advancing age when AD pathology appears in individuals free from dementia[175]. In this thesis, the assessment of biological active molecules in plasma was performed with the purpose to distinguish between different dementia subtypes. As mentioned above, AD dementia and VaD share many risk factors and therefore, the use of biomarkers marking different pathological processes may help to find the etiology of certain dementia subclasses. Several studies have been conducted to find blood-based biomarkers that are associated with dementia, but so far, the results have been contradictive[176]. Since a variety of cardiovascular risk factors including hypertension, smoking, dyslipidemia, and prevalent cardiovascular disease (CVD) all have been associated with the development of dementia[177], there has been a growing interest in linking cardiovascular biomarkers to incident dementia[178].

Atrial natriuretic peptide, Adrenomedullin, Endothelin and Somatostatin - Circulating biomarkers

Atrial natriuretic peptide (ANP) was first described in 1983-1984 as a cardiac hormone released by the atrium in response to atrial mechanical wall stress[179, 180]. Thereafter, ANP has been implicated in the pathophysiology of several cardiovascular diseases including heart failure, myocardial infarction, stroke and hypertension. By inhibition of aldosterone synthesis and renin secretion, ANP stimulates vasodilation and natriuresis. Hence, elevated plasma concentrations of ANP seen in individuals with hypertension and heart failure is considered as a compensatory mechanism aiming to lower the blood pressure level[181]. Whilst bioactive ANP is difficult to measure, recently developed assays have enabled the measurement of midregional pro- atrial natriuretic peptide (MR-proANP) which

might be more useful than ANP due to the lack of receptor binding, protein interactions and considerably longer half-life[182].

Adrenomedullin (ADM), a 52-amino acid and member of the calcitonin peptide family, is widely expressed in the body including cardiovascular, renal, pulmonary, cerebrovascular, gastrointestinal, and endocrine tissues[183]. It is predominantly secreted by endothelial and smooth muscle cells as response to vascular wall stress[184, 185]. By increasing the amount of nitric oxide (NO) and reducing endothelin (ET), ADM promotes vasodilation[185]. Several studies have shown that elevated levels of ADM stimulate natriuresis and diuresis which is suggested as a protective measure in response to elevated blood pressure[186, 187]. Hence, the plasma concentration of ADM is increased in individuals with hypertension, heart failure or arteriosclerosis, as compared with healthy subjects[188, 189]. Furthermore, ADM possess antihypertrophic, anti-apoptotic, antifibrotic, antioxidant, and angiogenesis effects[190]. Due to its low in vitro stability, ADM is difficult to measure in plasma. Therefore, the stable inactive precursor, midregional pro-adrenomedullin (MR-proADM), secreted in equimolar amounts to bioactive ADM is favorably measured[191]. In patients with myocardial infarction and heart failure, MR-proADM is an independent predictor of death[192, 193].

Endothelin 1 (ET-1), a 21-amino acid is a potent vasoconstrictor synthesized by endothelial and vascular smooth muscle cells in response to hypoxia and vascular strain. Endothelin has been emphasized as a marker of CVD as it stimulates inflammation and proliferation[194]. Several diseases including atherosclerosis, hypertension, chronic heart failure, and myocardial infarction have been associated with increased plasma concentration of endothelin[194, 195]. ET-1 exhibits a regulatory function by stimulating the secretion of other peptides such as ANP[196]. In the brain, ET-1 has been located in vascular endothelial and smooth muscle cells as well as in macrophages and neurons[197]. Elevated plasma concentrations of ET-1 have also been detected in patients with acute ischemic stroke[198] and in sepsis[199]. The precursor peptide C-terminal proendothelin-1 (CT-proET-1) is more stable and is therefore favorably measured[200].

Somatostatin (SST) was first discovered in the ovine hypothalamus in the 1970's. Since then, SST has been detected in a broad range of tissues including the pituitary gland, pancreas and CNS where it exhibits a regulatory function by inhibiting the secretion of serval hormones such as gastrin, secretin, vasoactive peptide, insulin and glucagon, thyrotropin, growth hormone, ACTH and prolactin. Within the brain, somatostatin modulates the neurotransmission by inhibiting the release of dopamine, serotonin and norepinephrine. Thus, it exhibits effects on cognition, locomotor activity, sensory and autonomic functions[201-204]. Somatostatin has two native bioactive forms, the 14 amino acid-containing form SST-14 located primarily in CNS and SST-28 produced in intestinal enteroendocrine cells[205]. Due to the short half-life in plasma and dual paracrine and endocrine functions, SST

is difficult to measure. Therefore, its precursor N-terminal prosomatostatin [1–64] (NT-proSST), which is more stable and correspond to SST secretion is measured[206, 207]. Elevated levels of plasma NT-proSST have recently been shown to independently predict the development of coronary artery disease and both all-cause and cardiovascular mortality[208].

Aims

- We sought to explore how resting and postural BP changes relate to incident dementia over a long-term follow-up

- We explored the longitudinal association of the vasoactive peptides midregional pro-atrial natriuretic peptide (MR-proANP), C-terminal endothelin-1 (CT-proET- 1) and midregional proadrenomedullin (MR- proADM) with dementia and subtypes among community-dwelling older adults

- We sought to assess the longitudinal association of circulating N-terminal prosomatostatin (NT-proSST) with incident dementia among community-dwelling older adults

- We aimed to evaluate the longitudinal association between use of beta blockers, as a class, and incident risk of all-cause dementia, vascular dementia, Alzheimer and mixed dementia

- We aimed to assess the predictive role of cognitive test results in regard to risk of mortality and rehospitalization in a Swedish prospective heart failure (HF) patient cohort

Material and methods

Study populations

Malmö preventive project, MPP

The Malmö Preventive Project (MPP) is a prospective population-based cohort funded in the early 1970s at Malmö University Hospital in purpose to explore CV risk factors, alcohol abuse, impaired glucose tolerance, and breast cancer[209]. Between 1974 and 1992, a total of 33,346 citizens living in Malmö were participating with an attendance rate of 71%. Participants were predominantly men (67%) born in 1921, 1926–1942, 1944, 1946 and 1948–1949. Participating women were born in 1926, 1928, 1930–1936, 1938, 1941–1942 and 1949[210]. Since male participants were enrolled more frequently during the first years of the study (1974-82) and female during the later period (1981-92), the follow-up period varies between gender[209]. At baseline, participants conducted a self-administrated questionnaire and underwent a physical examination to obtain data regarding hypertension, diabetes, obesity, hyperlipidemia, smoking, family history of CV disease and other potential CV risk factors. A comprehensive report of the baseline study protocol has been published elsewhere[110]. Between 2002 and 2006, a total of 18,240 of the surviving participants in MPP were re-examined in the MPP-Re-examination Study (MPP-RES). All individuals, participating in MPP and MPP-RES gave written informed consent and ethical approval has been given by the Regional Ethics Board in Lund, Sweden.

The heart and brain failure investigation study, HARVEST

The HeARt and brain failure inVESTigation study (HARVEST) is a prospective study undertaken in patients hospitalized for the diagnosis of HF in the city of Malmö, Sweden. The overall aim of the study is to find new mechanisms and therapeutic targets causally associated with progressing HF, thus suitable for further drug development and to gain knowledge of how to optimally treat HF patients to avoid concomitant cognitive dysfunction or dementia. Upon hospitalization and following admission to the heart failure clinic and internal medicine wards, study participants are examined with anthropometric measurements and blood samples are drawn after overnight fast. To explore the cognitive function, patients are examined with cognitive tests including Montreal Cognitive Assessment (MoCA), A quick cognitive test (AQT), Cube copying test, Trail making A and B (TMT A

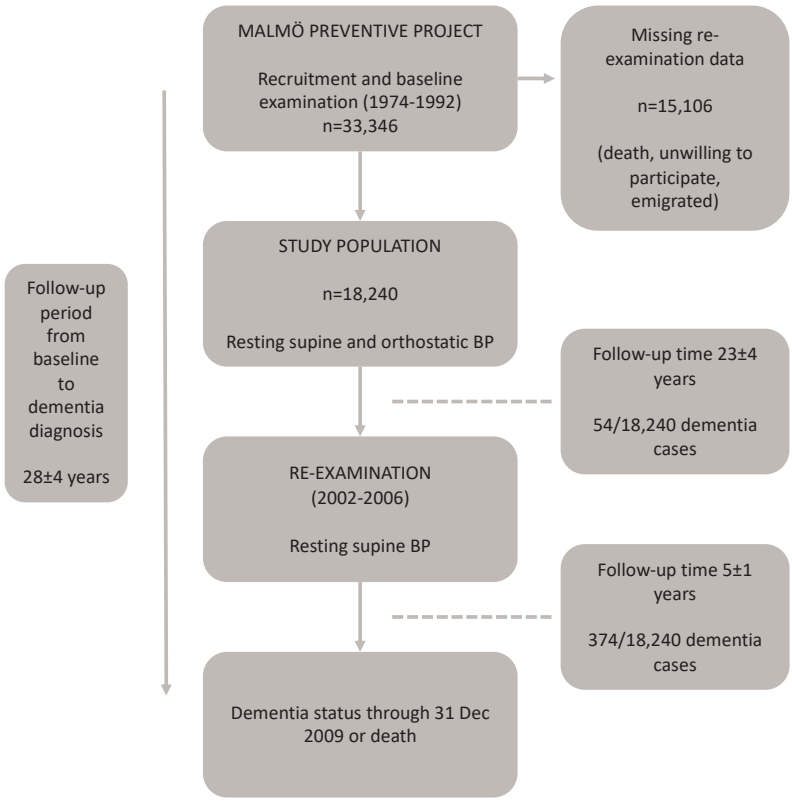
and B), the Symbol digit modalities test (SDMT) and the Stroop Test. Environmental, socioeconomic, and lifestyle factors are characterized by a self-reported questionnaire. To assess the heart function all participants, undergo examination with transthoracic echocardiogram (TTE). The inclusion criteria are admission to the department of internal medicine or cardiology for treatment of newly diagnosed or worsened chronic HF. The only exclusion criterion is the inability to deliver oral or written consent and for patients with severe cognitive impairment, defined as MoCA score <13 points, the relatives are informed and asked for permission on the patient's behalf. Between March 2014 and February 2019, a total of 400 consecutive patients hospitalized for HF were included and underwent clinical examination (mean age 75±12, 68 % men). Surviving participants are re-invited to participate in a re-examination 4 months after hospital discharge. The re-examination is performed according to the same protocol as baseline screening. The study is approved by the Ethical Review Board at Lund University, Sweden (DNR 2013/360 (2013-08-06), DNR 2014/48 (2014-03-18), DNR 2015/404 (2015-06-09) and DNR 2016/68 (2016-01-29) and is on-going since April 2014.

Paper-specific methods

Paper I

In this paper, we measured the longitudinal association between resting systolic BP (SBP), diastolic BP (DBP), postural BP response and orthostatic hypotension (OH) with the risk of developing dementia. Enrolled participants were individuals participating in MPP-RES between 2002 and 2006 (n=18,240). Variables with missing data, which was present in 3 to 365 cases, were excluded. Out of four-hundred seventy-one cases of dementia registered in the Swedish national patient register (SNPR), 428 cases were validated dementia diagnoses including; 142 AD dementia, 96 VaD, 114 Mixed dementia, 38 LBD/Parkinson dementia, 4 FTD, 34 unspecified type. Of these cases, 54 individuals were diagnosed with dementia before the re-examination in MPP and therefore classified as prevalent dementia cases. 374 individuals were diagnosed between the re-examination and Dec 31, 2009 and classified as incident dementia diagnoses. The 54 participants with prevalent dementia diagnosis at rescreening were excluded in analyses aiming the rescreening-to-dementia risk, see **Figure 1**. To investigate if BP changes may increase dementia risk, delta values for resting SBP and DBP were calculated between MPP baseline and MPP-RES. The follow-up time was calculated between MPP baseline and MPP-RES and the date of the dementia diagnosis, death, or end of follow-up on Dec 31, 2009. In order to test the increase of dementia risk between levels of BP, the BP derived parameters were stratified into quartiles and used in the statistical models.

Figure 1. Malmö Preventive Project and re-screening program



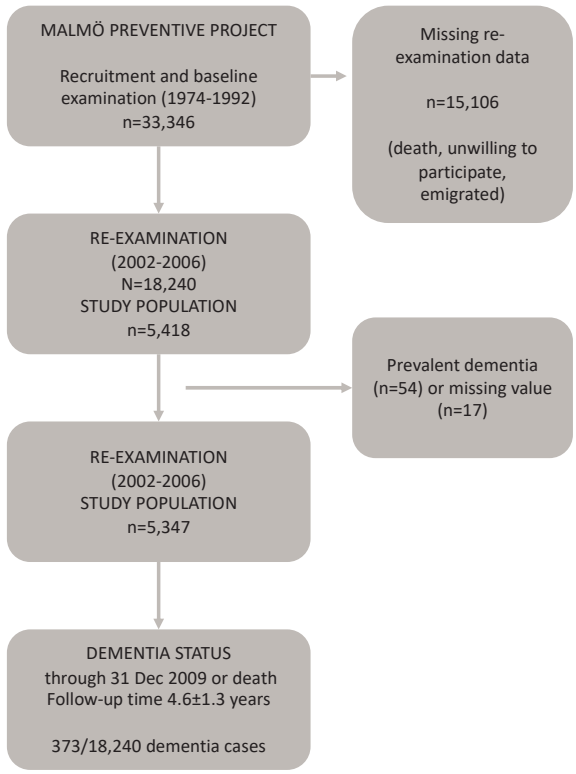
Paper II and III

In these two papers we studied whether biomarkers associated with vascular disease (MR- proANP, CT-proET-1, MR-proADM and NT-proSST) would predict incident dementia, in particular of vascular type. To test this hypothesis, we evaluated the incidence of all-cause dementia and its main subclasses in relation to plasma levels of the four biomarkers in 5, 418 individuals participating in MPP-RES.

Baseline level of all biomarkers were measured in frozen plasma in all participants who were diagnosed with dementia during follow-up, and in a random sample of 5,100 individuals of the cohort. Fifty-four individuals were diagnosed with dementia before the MPP-RES and 17 had missing values on different co-variates yielding a study sample of 5, 347 individuals. Of these, three-hundred-and- seventy-three individuals were diagnosed with incident dementia retrieved from a period of

at least 30 days after the screening examination and blood sampling to Dec 31, 2009, see **Figure 2**. The follow up period from inclusion in MPP-RES to the end of follow up was 4.6 ± 1.3 years.

Figure 2. Malmö Preventive Project and re-screening program

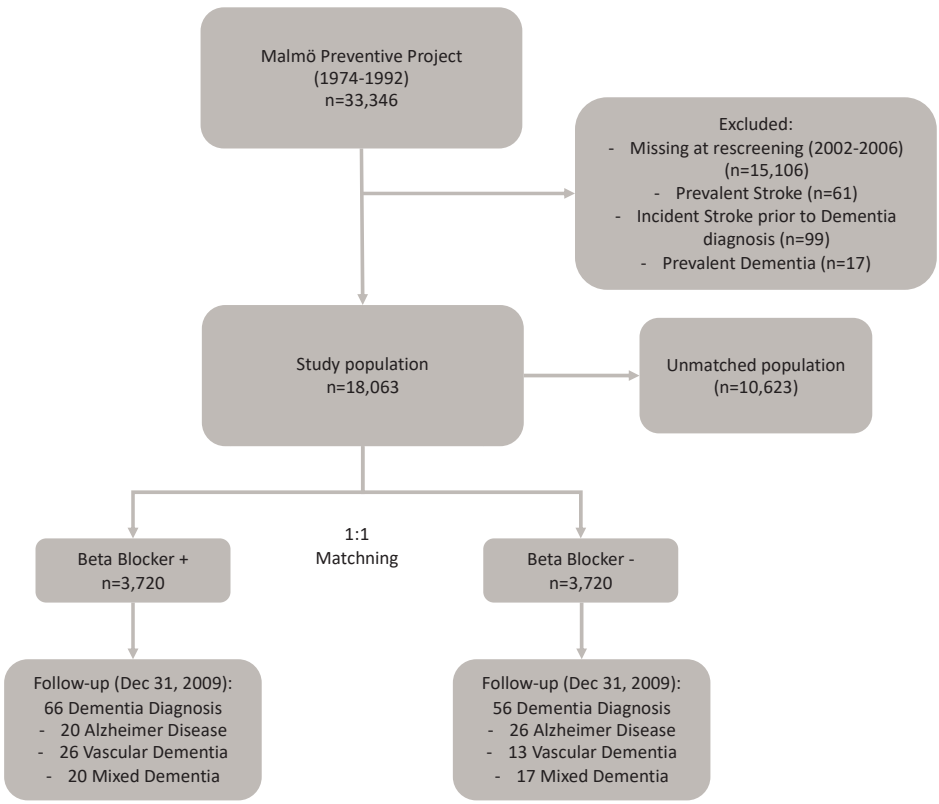


Paper IV

In **Paper I** we found that a decline in blood pressure between middle-and advanced age, and lower BP in advanced age were independent risk factors of incident dementia[211]. Prior studies have shown that blood pressure reduction causes a decline in cerebral perfusion, which has previously been emphasized as an

important factor in the pathology of vascular dementia[212]. Hence, antihypertensive treatment (AHT) which is commonly used among elderly individuals has been longitudinally linked to cognitive decline[154, 155]. As treatment with beta blockade (BB) is recommended as first–step medication in hypertensive patients we wanted to explore whether BB might increase the risk of dementia in MPP-RES. BB use was ascertained at MPP-RES between 2002-2006. Patients with prevalent stroke (n=61), incident stroke prior to dementia diagnoses (n=99), and prevalent dementia (n=17), were excluded from the analyses. In a propensity score matching procedure, 7,440 representative individuals were included and represent the current study population. The study population was separated into 2 groups (**Figure 3**) with an equal number of patients including BB users (n=3,720) and non-users (n=3,720). In the unmatched population, BB users were more frequently diabetic and more frequently users of angiotensin converting enzyme inhibitors, diuretics, aspirin, nitroglycerine and statins. After matching, there were no differences in the baseline characteristics between the two groups, with all standardized mean differences below 0.10.

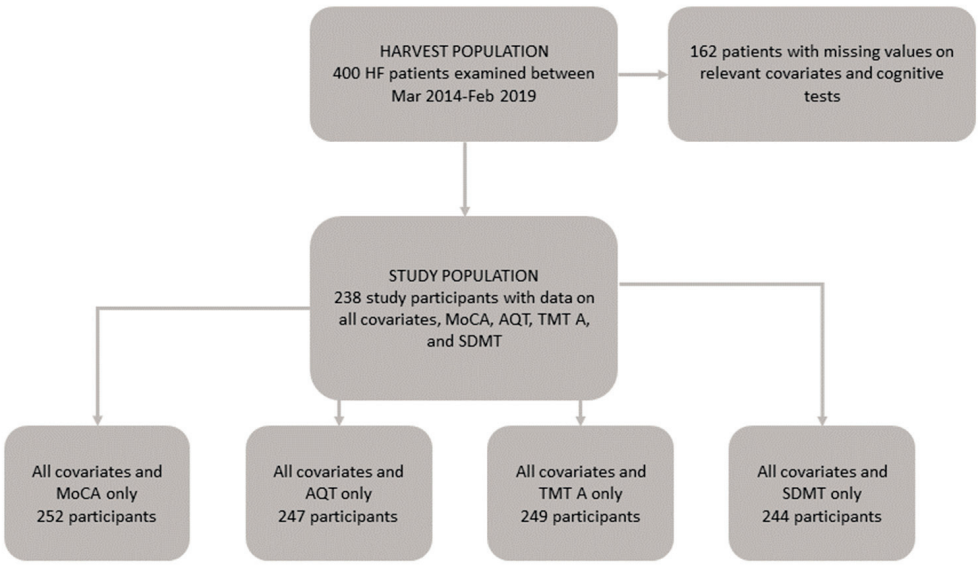
Figure 3. Flow diagram of the study population in Paper IV



Paper V

Between March 2014 and February 2019, a total of 400 consecutive patients hospitalized for HF were included and underwent clinical examination. Cognitive testing in the HARVEST study was first initiated Jan 2015 and of the 400 study participants, 162 patients had missing values on relevant covariates and cognitive tests, rendering a study population of 238 eligible participants, see **Figure 4**. The study was approved by the Ethical Review Board at Lund University, Sweden. A written informed consent was obtained from all participants or relatives as described above. Mortality was defined as death by any cause (total mortality) and was retrieved from the National Board of Health and Welfare's Cause of Death Register[213]. Data regarding rehospitalization were retrieved from electronical medical charts accessible through the patient's unique national statistical number in the regional hospital database (Melior, Siemens Health Services, Solna, Sweden).

Figure 4. Flow diagram of the study population in Paper V



Blood pressure measurements

In MPP baseline examination between 1974 to 1992, BP (mmHg) was measured manually with a mercury sphygmomanometer positioned around the right arm supported at the heart level[209]. SBP was defined by the 'phase I' and the DBP was defined by the 'phase V' Korotkoff sounds[214]. Supine BP was measured twice after 10 minutes of rest in lying position and the mean value of the two measurements was calculated. To obtain postural BP response, the participants were asked to stand up and new BP measurements were assessed twice after 1 minute of standing position. In MPP-RES, an automated sphygmomanometer was used and BP was only assessed in supine position. All obtained values were rounded up to the nearest integer. In the HARVEST study, trained nurses measured blood pressure (BP) using a validated automated BP monitor. Hypertension was defined as either systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. In MPP, OH was defined as standing SBP decrease ≥20 mmHg and/or DBP decrease ≥10 mmHg after 1 minute in standing position[215].

Retrieval of biomarkers

In **Paper II**, plasma concentrations of C-terminal endothelin-1 precursor fragment (CT-proET-1), the mid-regional fragments of pro-adrenomedullin (MR-proADM) and pro-atrial natriuretic peptide (MR-proANP) were measured from blood samples that had been frozen at –80℃ in MPP-RES. Immunoluminometric sandwich assays were used targeting amino acids in the mid-regions of the respective peptide (Thermo Scientific B·R·A·H·M·S CT-proET-1 KRYPTOR, Thermo Scientific B·R·A·H·M·S MR-proADM KRYPTOR and Thermo Scientific B·R·A·H·M·S MR-proANP KRYPTOR) (BRAHMS, Hennigsdorf, Germany) respectively[182, 200, 216].

In **Paper III**, the plasma level of the stable precursor of somatostatin, N-Terminal pro-somatostatin (NT-proSST) was estimated using the chemiluminescence/coated tube format (BRAHMS GmbH)[217] with a detection limit of 4 pmol/L. The variation of the interlaboratory coefficient was 20% at 18 pmol/L, 10% at 50 pmol/L and <6% for above 100 pmol/L. The assessment of plasma total cholesterol, high-density lipoprotein cholesterol, triglycerides was received according to standard procedures at the Department of Clinical Chemistry at Malmö University Hospital. The Friedewald equation and the Beckman Coulter modified Jaffe procedure were used, respectively, to estimate low-density lipoprotein cholesterol and serum creatinine[218].

Assessment of dementia diagnoses and cognitive function

Incident dementia diagnoses were assessed from the Swedish National Patient Register (SNPR) which contains all in-patient care diagnoses in Sweden and outpatient visits including day surgery and psychiatric care from both private and public caregivers recorded from year 1987 to 2001. Primary care is not covered in the SNPR[219]. Dementia diagnoses were coded according to the International Classification of Diseases (ICD 8th, 9th, and 10th revisions) and validated after a comprehensive review of medical records, laboratory results and neuro imaging information. The final diagnosis was made by a research physician at the memory Clinic at Malmö University Hospital and in unclear cases a specialized geriatrician was consulted. The Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-IIIR) was used to diagnose All-cause dementia[220]. For the diagnoses of AD and VaD, DSM-IV criteria were applied and when the clinical and neuroimaging presentation were consistent with both AD and VaD, the diagnose of mixed dementia was applied[20].

In **Paper V**, the HARVEST participants underwent the cognitive tests within 3 days from hospital admission. The tests assessed global cognition (Montreal Cognitive Assessment (MoCA))[221], cognitive speed (A Quick Test of Cognitive speed (AQT))[222], visual attention and task switching (Trailmaking A (TMT A))[223] and information processing (the digit symbol coding test (SDMT))[224]. The tests were administered by trained nurses.

MoCA is a one-page global cognitive test where the cognitive performance is ranked from 0 to 30 points (30 is the highest possible score)[221]. The test evaluates 8 cognitive domains including visuospatial, executive, short and long-term memory recall, attention, language, abstraction and orientation. In the current study, a score below 23 points was regarded as cognitive impairment [221, 225]. In MoCA, the memory recall assignment contains 2 learning trials of 5 nouns where the subject is instructed to repeat the words directly (short-term recall) and after 5 minutes (long-term recall). The visuospatial cognitive ability is assessed using a cube and clock-drawing task. The executive function is partly assessed using a task where the subject is instructed to draw lines between circles numbered 1- 5 and circles with letters A-E in an ascending pattern (i.e., 1-A-2-B-3-C, etc.). The executive function is also examined by a phonemic fluency task, and a two-item verbal abstraction task. To assess the orientation ability, the subject is instructed to recall the current date, month, year, place and city. Language is evaluated by a three-item confrontation naming task where the subject is assigned to name 3 portrayed animals. The language ability is also assessed in a task of repetition of two syntactically complex sentences. Finally, attention is assessed by three tasks; repetition of a list of digits forward and backwards, a serial subtraction task and a target detection task, **Figure 5**.

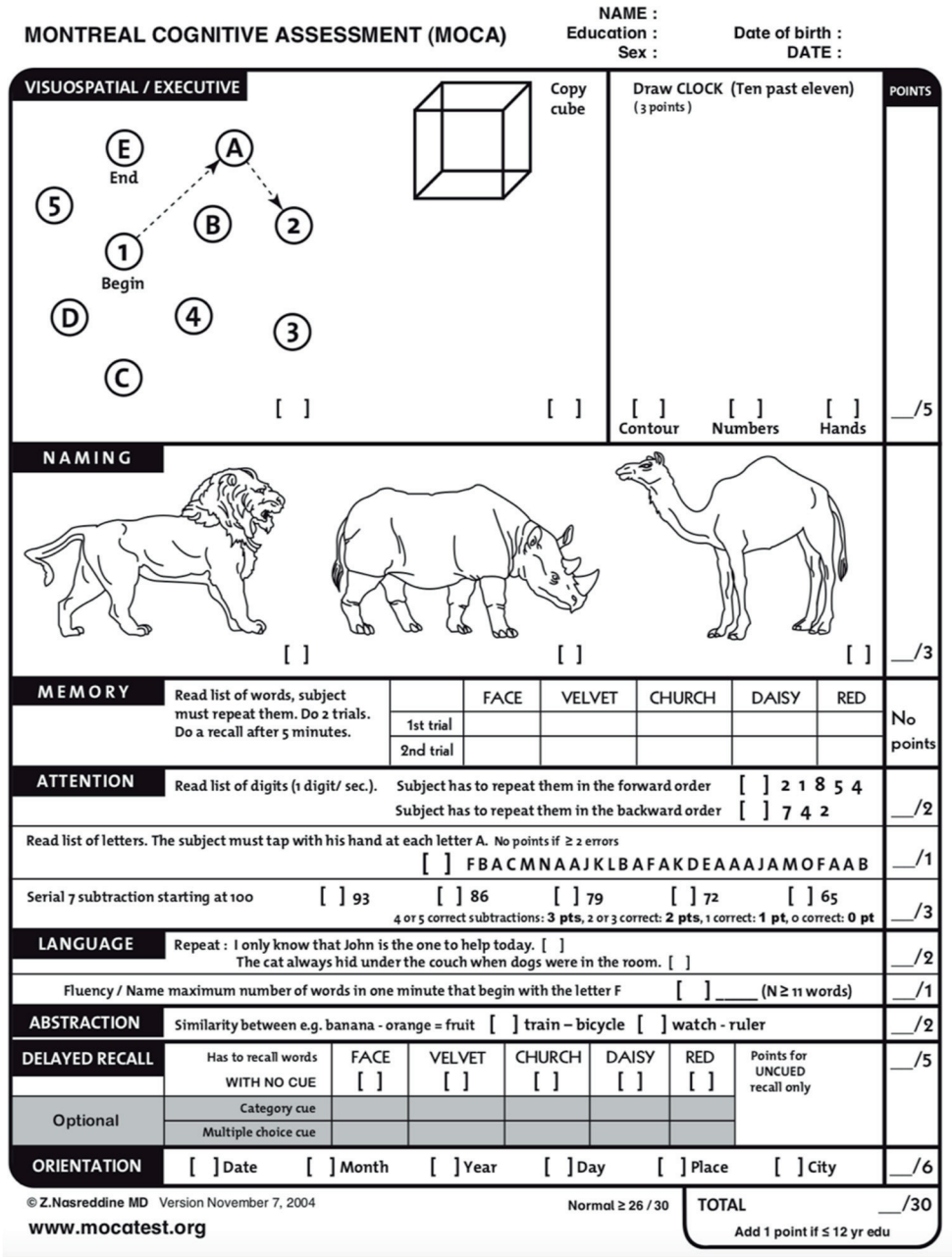
In AQT, the perception and overall cognitive speed are assessed. The test includes 3 parts with 40 visual stimuli where the first two parts measure the time to name the color of 40 squares and the shape of 40 geometric figures respectively. In the third test part the subject is instructed to combine 40 geometric figures with colors as fast as possible (circles, squares, rectangles, or triangles, colored red, black, yellow, or blue). The AQT score in part 3 is regarded as the number of seconds it takes to complete the task. In **Paper V** we only assessed the third part. Normal time limit is expected to be below 70 seconds based on data from 300 normally aging adults (ages 15-95)[226, 227].

The Trail making test consists of 2 parts (A and B) which together assess executive functions, visual search, scanning, speed of processing, mental flexibility[223]. In part A (TMT A) the subject is instructed to draw lines between circles numbered 1-25 in an ascending order. In part B (TMT B), the subject is instructed to draw lines between circles numbered 1- 14 and circles with the letters A-L in an ascending pattern (i.e., 1-A-2-B-3-C, etc.). The score in both parts are regarded as the number of seconds it takes to complete the task. Due to a high amount of missing data in part B (n=33), **Paper V** only assesses part A. Normative data for TMT A in the age category of 70-74 years in regard to educational level (0-12 years, and >12 years) has previously been shown as 42 (SD 15,5) and 40 (SD 14,5) seconds respectively[223].

The SDMT is used to evaluate attention, visual scanning, motor speed and associative learning[224, 228]. Subjects are required to repeatedly pair 9 specific symbols to a specific number from 1-9. The obtained score is ranged from 0-110 and is regarded as the correct number of associations within 90 seconds[229].

All tests were performed by trained nurses interviewing the patients in an environment free from disturbance.

Figure 5. MoCA test



Statistics

Paper I

Group differences in continuous variables between dementia-positive and -negative individuals were compared using One-Way ANOVA test, whereas categorical variables were compared using Pearson's Chi-square test. The longitudinal associations of incident dementia with BP recorded during baseline and rescreening examinations, including data on postural i.e. orthostatic systolic (SBP) and diastolic (DBP) BP reaction at baseline were studied. Cox regression model was applied entering supine SBP/DBP at baseline or re-examination, categorical OH, orthostatic SBP/DBP reaction at baseline, difference in SBP/DBP between baseline and re-examination, and prevalent hypertension defined as SBP ≥140 mmHg or DBP ≥ 90 mmHg or self-reported antihypertensive treatment as independent variables. The adjusted model was built by entering age, gender, antihypertensive treatment, diabetes, smoking, prevalent CV disease, and plasma-cholesterol as covariates. Further, BP related variables (orthostatic SBP/DBP reaction, supine SBP/DBP at re-examination, and SBP/DBP difference between baseline and re-examination) were stratified into quartiles and used for Kaplan–Meier survival analysis, and as an independent variable for Cox regression analysis in order to test the risk increment across the quartiles of BP derived parameters. The missing data ranged from 3 to 365 cases for different variables, and the cases were not included in the respective analyses. All analyses were performed using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA). All tests were two- sided, whereby significant.

Paper II and III

Group differences in continuous variables between dementia-positive and dementia-negative individuals were compared using one-way ANOVA test, whereas categorical variables were compared using Pearson's Chi-square test. The distribution of all four biomarkers was right-skewed and log-transformation was performed. Cox regression model was applied and log-transformed and standardized values of MR-proANP, CT-proET-1, MR- proADM and NT- proSST were entered as independent variables. The adjusted model was built by entering age, gender, systolic blood pressure (SBP), antihypertensive treatment, smoking, diabetes, plasma high-density lipoprotein (HDL) and prevalent stroke as covariates. Further, the biomarkers were stratified into quartiles and used for Kaplan–Meier survival analysis. Then, the quartiles were used as an independent variable for Cox regression analysis to test the risk increment across the quartiles of tested biomarkers. The time variable was calculated as follow-up time between screening and date of dementia diagnosis, death, or end of follow-up through 31 December 2009. All analyses were performed using IBM SPSS Statistics version 23 (SPSS

Inc., Chicago, IL, USA). All tests were two- sided, whereby $P < 0.05$ was considered statistically significant.

Paper IV

Quantitative variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution. Qualitative variables were summarized as frequency and percentage. In order to compare outcomes between beta-blocker users (BB+) and beta-blocker non-users (BB-), a propensity score matching procedure was performed using a multivariable logistic model with 8:1 greedy matching algorithm with no replacement[230]. The adequacy of covariate balance in the matched sample was assessed via standardized mean differences between the two groups, with differences of less than 10% indicating a good balance[231]. Patients for whom no match was found, were discarded from the matched analyses. Rates of overall survival were estimated by means of the Kaplan–Meier method and were compared between beta-blocker users and non-users with the use of the log-rank test. Cox regression model was applied to estimate hazard ratios with 95% confidence interval (HR 95%CI). Two types of models were performed: the first predictive model of dementia status was performed with beta-blocker use as independent variable adjusted only for propensity score. The second model was performed in the same way, adding incident heart failure, incident atrial fibrillation and incident coronary event as covariates. Only the BMI variable had missing values (96 patients, 0.53%). Missing values were handled with multiple imputation technique using chained equations[232]. All variables used as covariate in the matching procedure were included in the imputation model. 2-tailed P-values less than 0.05 were considered significant. The statistical analysis was performed using IBM SPSS Statistics v23.0 software (SPSS Inc. Chicago, Illinois, USA).

Paper V

The variables are presented as means (±standard deviation (SD)) or median (25%-75% interquartile range). Cox regression model was applied to estimate proportional hazards with 95% CI for each cognitive test per SD increase. Continuous standardized values of each cognitive test were entered as independent variables in separate models. In order to increase the power of each model, the event of death or rehospitalization was entered in separately for each cognitive test. Further, the cognitive test results were stratified into quartiles and used for Kaplan–Meier survival analysis. Then, the quartiles were used as an independent variable for Cox regression analysis to test the risk increment across the quartiles of the cognitive tests. The adjusted model 1 included age and sex. The adjusted model 2 was built by entering age, sex, body-mass index, systolic blood pressure, NYHA-class at admission, diabetes, educational level, prevalent atrial fibrillation and smoking as

independent variables. The time variable was calculated as follow-up time between screening and date of first rehospitalization or death, respectively. All analyses were performed using SPSS Windows version 25.0 and a p-value of 0.05 was considered statistically significant in the Cox regression analysis.

Manuscript specific results

Paper I

At baseline, study participants that developed dementia during the follow-up period (n=428) were older, more likely to be women and had higher probability of diabetes. Dementia participants had higher supine SBP and DBP compared to the rest of the cohort, and demonstrated more pronounced SPB fall and less pronounced DBP increase upon standing. At rescreening, dementia participants had lower supine SBP and DBP, while the proportion of antihypertensive treatment was slightly higher in the dementia-positive group (**Table 6**).

Table 6. Characteristics of study participants (n=18,240) at baseline and reexamination stratified according to dementia diagnosis during follow-up period

Characteristic	Dementia positive n=428	Dementia negative n=17,812	*p-value*
Baseline			
Age (years)	50±5	45±7	<0.001
Sex % (male)	59	64	<0.001
Current smoker %	40	37	0.2
BMI (kg/m2)	25±3	24±3	0.91
Supine systolic BP (mmHg)	131±16	127±14	<0.001
Supine diastolic BP (mmHg)	86±10	85±9	<0.001
Antihypertensive treatment %	7	4	0.003
Hypertension %	44.1	34.4	<0.001
Orthostatic systolic BP reaction (mmHg)	-2.8±7	-1.4±7	<0.001
Orthostatic diastolic BP reaction (mmHg)	+1.7±5	+2.5±5	<0.001
Diabetes %	4.4	3.1	0.018
Plasma cholesterol (mmol/l)	6.0± 1	5.5± 1	<0.001

Re-examination			
Age (years)	73±5	68±6	<0.001
Current smoker, %	14	14	1.0
Systolic BP (mmHg)	143±21	145±20	0.034
Diastolic BP (mmHg)	81±11	84±11	<0.001
Antihypertensive treatment %	43	38	0.057
Hypertension %	71.9	72.2	0.9
Diabetes %	20	11	0.18
Plasma cholesterol (mmol/l)	5.7±1.1	5.6±1.1	0.62

Values are displayed as mean ± SD or frequency in percent. BMI body mass index, BP blood pressure

Postural BP decrease and supine BP at baseline versus dementia

In the multivariable Cox regression model (**Table 7**), postural DBP decrease, but not SBP decrease at baseline was significantly associated with the risk of developing dementia [Hazard ratio (HR) per 10 mmHg: 1.22; 95% confidence interval (CI) 1.01–1.44, p = 0.036, and 1.02; 0.89–1.15, p = 0.74, respectively]. Supine SBP and DBP at baseline were not associated with increased incidence of all-cause dementia, neither as a continuous variable (HR per 10 mmHg: 1.04; 95% CI 0.98–1.10, p = 0.19, and 1.05; 95% CI 0.95–1.16, p = 0.30, respectively). However, both elevated SBP and DBP at baseline conferred to higher risk of incident vascular dementia (HR per 10 mmHg: 1.23; 95% CI 1.12–1.35, p <0.001, and 1.48; 95% CI 1.27–1.68, p <0.001, respectively).

Table 7. Relationship between blood pressure levels at baseline and re-examination and dementia risk

Characteristic	HR, 95 % CI * per 10 mmHg)	*p-value*
Baseline supine SBP (n= 17, 912)	1.04 (0.98-1.10)	0.19
Baseline supine DBP (n= 17, 909)	1.05 (0.95-1.16)	0.30
Orthostatic SBP reaction (n= 17, 884)	1.02 (0.89-1.15)	0.74
Orthostatic DBP reaction (n= 17, 875)	1.22 (1.01-1.44)	0.036
Orthostatic hypotension# (383/17, 492)	1.18 (0.73-1.89)	0.51
Re-examination SBP (n= 18, 044)	0.94 (0.89-0.99)	0.011
Re-examination DBP (n= 18, 043)	0.87 (0.78-0.96)	0.006
SBP decrease between baseline and re-examination (n= 17, 719)	1.07 (1.03-1.12)	0.002
DBP decrease between baseline and re-examination (n=17, 715)	1.16 (1.08-1.25)	<0.001

HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure. *Adjusted for age, gender, anti-hypertensive treatment, smoking, diabetes, prevalent cardiovascular disease, and plasma-cholesterol. #Orthostatic hypotension is a categorical variable.

Supine BP at re-examination versus dementia

At re-examination, higher SBP and DBP values were associated with lower risk of dementia (HR per 10 mmHg: 0.94; 95% CI 0.89–0.99, p = 0.011; and 0.87; 0.78–0.96, p = 0.006, respectively; **Table 7**). As shown in **Table 8**, individuals with lowest was associated with increased dementia risk (HR 1.48; 95% CI 1.12–1.94, p = 0.006) compared to individuals with highest SBP.

Longitudinal changes in BP versus dementia

SBP decrease between baseline and re-examination was associated with increased risk of dementia (HR 1.07; 95% CI 1.03–1.12, p = 0.002) and so was DBP decrease between baseline and re-examination (HR 1.16; 95% CI 1.08–1.25, p = 0.001; **Table 7**).

Table 8. Associations between dementia and blood pressure variations across quartiles of blood pressure-derived parameters

Quartiles	**n**	**HR, 95 % CI***	***p-value***
Orthostatic DBP reaction (baseline)			
Q1 (≥7.5 mmHg)	3161	Reference	
Q2 (2.5 to 5.0 mmHg)	6995	1.06 (0.79-1.43)	0.68
Q3 (0 mmHg)	4834	1.03 (0.75-1.41)	0.86
Q4 (≤ -2.5 mmHg)	2885	1.41 (1.02-1.94)	0.036
p for trend		0.072	
SBP at re-examination			
Q1 (≥158 mmHg)	4466	Reference	
Q2 (143 to 157 mmHg)	4638	1.16 (0.87-1.54)	0.31
Q3 (131 to 143 mmHg)	4480	1.11 (0.83-1.45)	0.49
Q4 (≤130 mmHg)	4444	1.48 (1.12-1.94)	0.006
p for trend	0.032		
DBP at re-examination			
Q1 (≥91 mmHg)	4480	Reference	
Q2 (83 to 90 mmHg)	4466	1.10 (0.81-1.49)	0.53
Q3 (77 to 83 mmHg)	4632	1.15 (0.85-1.55)	0.37
Q4 (≤76 mmHg)	4449	1.33 (1.00-1.78)	0.050
p for trend	0.24		

HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure. Adjusted for age, gender, anti-hypertensive treatment, smoking, diabetes, prevalent cardiovascular disease, and plasma-cholesterol

Paper II

Study participants who developed dementia (n=373) were older, more likely to be female, had higher plasma concentration of HDL, and higher proportion of statin treatment, and lower SBP compared with individuals free from dementia. Plasma concentrations of MR-proANP, CT-proET-1 and MR-proADM were higher in participants who developed dementia (**Table 9**).

Table 9. Characteristics of the study population (*n*=5 347)

Characteristics	Dementia positive n=373	Dementia negative n=4, 974	*p-value*
Age (years)	73±5	69±6	<0.001
Sex (% male)	58	71	<0.001
Current smoker, n (%)	48 (13)	795 (16)	0.087
Supine systolic BP (mmHg)	143±21	146±21	0.006
Supine diastolic BP (mmHg)	81±11	84±11	<0.001
Heart rate (bpm)	71±12	71±12	0.541
Antihypertensive treatment, n (%)	159 (43)	1948 (39)	0.102
Statin treatment, n (%)	99 (27)	957 (19)	0.001
Prevalent stroke, n (%)	43 (12)	251 (5)	<0.001
Plasma cholesterol (mmol L^{-1})	5.6±1.1	5.5±1.1	0.67
Plasma LDL (mmol L^{-1})	3.6±1	3.6±1	0.66
Plasma HDL (mmol L^{-1})	1.44±0.4	1.37±0.4	<0.001
Diabetes, n (%)	620 (12)	47 (13)	0.523
MR-proANP (pmol/l)	151±85	123±82	<0.001
MR-proADM (nmol/l)	0.80±0.23	0.74±0.23	<0.001
CT-proET-1 (pmol/l)	75±21	71±19	<0.001

BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MR-proANP, midregional pro-atrial natriuretic peptide; MR-proADM, midregional proadrenomedullin; CT-proET-1, C-terminal endothelin-1.

In the multivariable-adjusted Cox proportional hazard models, higher levels of MR-proANP were significantly associated with increased risk of all- cause and vascular dementia. None of the biomarkers showed significant association with Alzheimer dementia, but higher MR-proANP tended to predict mixed dementia, see **Table 10**.

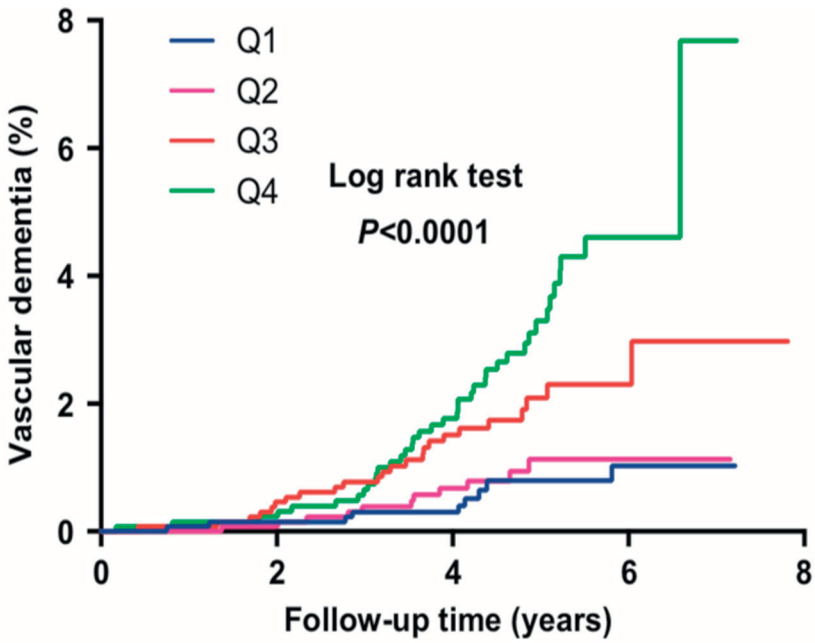
Table 10. Relations between microcirculatory biomarkers (MR-proANP, CT-proET-1, and MR-proADM) and risk of dementia in multivariable-adjusted Cox regression model

Biomarkers	Type of dementia	
	aHR (95%CI)	P value
	All-cause dementia (n=373)	
MR-proANP	1.20 (1.07-1.36)	0.002
CT-proET-1	1.04 (0.93-1.17)	0.51
MR-proADM	1.00 (0.89-1.14)	0.91
	Alzheimer dementia (n=120)	
MR-proANP	0.97 (0.77-1.21)	0.77
CT-proET-1	0.94 (0.77-1.16)	0.56
MR-proADM	0.87 (0.70-1.07)	0.19
	Vascular dementia (n=83)	
MR-proANP	1.52 (1.21-1.89)	<0.001
CT-proET-1	1.22 (0.98-1.53)	0.073
MR-proADM	1.20 (0.94-1.52)	0.14
	Mixed dementia (n=102)	
MR-proANP	1.25 (0.99-1.58)	0.057
CT-proET-1	1.07 (0.85-1.34)	0.57
MR-proADM	0.94 (0.74-1.19)	0.63

CI, confidence interval; CT-proET-1, C-terminal endothelin-1; aHR, adjusted hazard ratio; MR-proADM, midregional proadrenomedullin; MR-proANP, midregional pro-atrial natriuretic peptide. Adjusted for age, gender, systolic blood pressure, anti-hypertensive treatment, smoking, diabetes, and plasma-HDL, and prevalent stroke. All biomarker plasmatic concentrations were log-transformed.

The risk of vascular dementia increased across quartiles of CT-proET-1 (p for linear trend = 0.028) with a distinct cut-off point between second and third quartile. The two highest quartiles of CT-proET-1 predicted vascular dementia with a cut-off value at 68 pmol L^{-1} (Q3–Q4, 68– 432 pmol L^{-1} vs. Q1–Q2, 4–68 pmol L^{-1}; HR: 1.94; 95%CI: 1.12–3.36), see **Figure 6**.

Figure 6. Kaplan–Meier curves for vascular dementia cumulative incidence from re-examination (2002–2006) to the end of follow-up (31 December 2009) among 5337 participants in MPP stratified according to quartiles of CT-proET-1



Q1	1334	1306	1020	336	0
Q2	1334	1297	1011	239	0
Q3	1335	1283	998	153	0
Q4	1334	1218	988	71	0

Paper III

In the crude Cox proportional hazard model, NT- proSST predicted both all-cause and vascular dementia (**Table 11**). In the multivariable-adjusted model, higher levels of NT-proSST were significantly associated with an increased risk of vascular dementia only, whereas no significant association was observed with incident Alzheimer dementia, all-cause or mixed dementia.

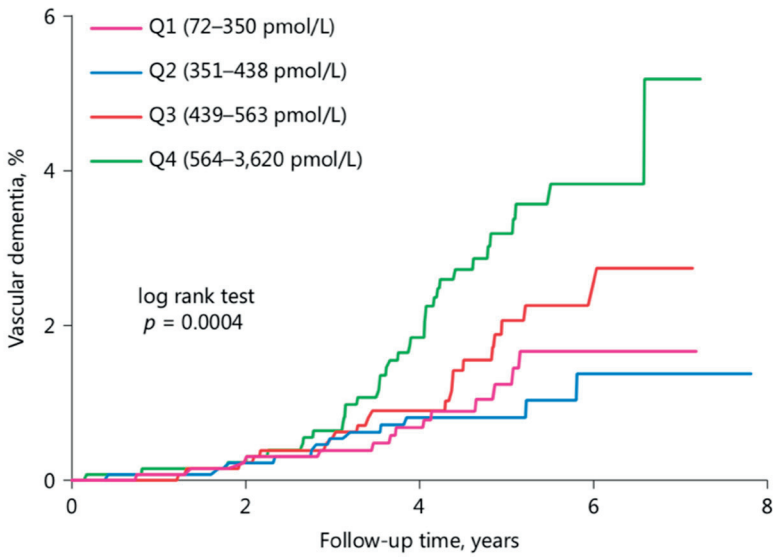
Table 11. Relations between the plasma level of N-terminal pro-somatostatin and risk of dementia in crude and multivariable-adjusted Cox regression model among older adults (*n*=5,347)

Type of dementia Hazard ratio (95%CI)	P value
All-cause dementia (n=373)	
Model 1: 1.20 (1.08-1.33)	<0.001
Model 2: 1.00 (0.90-1.11)	0.996
Alzheimer dementia (n=120)	
Model 1: 12 (0.94-1.35)	0.21
Model 2: 0.96 (0.79-1.17)	0.68
Vascular dementia (n=83)	
Model 1: 1.60 (1.32-1.95)	<0.001
Model 2: 1.29 (1.05-1.59)	0.016
Mixed dementia (n=102)	
Model 1: 1.14 (0.93-1.38)	0.20
Model 2: 0.91 (0.74 -1.11)	0.35

Model 1: Adjusted for gender, age
Model 2: Adjusted for age, gender, body mass index, systolic blood pressure, anti-hypertensive treatment, smoking, diabetes, plasma HDL, and prevalent stroke. Plasma concentration values of N-terminal prosomatostatin were log-transformed. Hazard ratio is reported as per 1 SD.

As shown in **Figure 7**, the risk of incident vascular dementia increased distinctly in the highest (4th) quartile of plasma NT-proSST levels, whereas it was comparable between the 1st and 2nd quartiles. Accordingly, participants within the 4th quartile (>563 pmol/L) of NT- proSST demonstrated a significantly higher risk of vascular dementia (HR 1.66; 95% CI 1.05–2.63; $p = 0.029$) compared with lower quartiles.

Figure 7. Kaplan-Meier curves for cumulative vascular dementia incidence (*n* = 83) from rescreening (2002–2006) to the end of follow-up (December 31, 2009) among 5, 347 participants of Malmö Preventive Project stratified according to quartiles of NT- proSST between baseline (2002–2006) and to the end of follow-up; Q1 72–350 pmol/L; Q2 351–438 pmol/L; Q3 439–563 pmol/L; Q4 564–3620 pmol/L



Number at risk					
Q1	1,331	1,289	996	234	0
Q2	1,339	1,292	1,018	201	0
Q3	1,335	1,280	1,017	210	0
Q4	1,336	1,246	989	164	0

Paper IV

Baseline characteristics

The study population included 18, 063 patients (mean age was 68.2±5.8 years; 63.4% males). Study participants who received dementia diagnosis were older (73.1 vs 68.1 years), more likely to be women (43.8% vs 36.5%) and more frequently treated with acetylsalicylic acids (ASA) and statins (**Table 12**).

Table 12. Baseline demographic and clinical characteristics of study population

Baseline Characteristics	Selected population (n=18,063)	Dementia positive (n=249)	Dementia negative (n=17,814)
Age, mean±SD	68.2±5.8	73.1±4.4	68.1±5.7
BMI, mean±SD	27.2±4.4	25.7±3.9	27.2±4.4
Gender n (%)			
Male	11,447 (63.4)	140 (56.2)	11,307 (63.5)
Female	6,616 (36.6)	109 (43.8)	6,507 (36.5)
Current smoker n (%)	2,453 (13.6)	32 (12.9)	2,421 (13.6)
Medical history n (%)			
Diabetes	2,004 (11.1)	31 (12.4)	1,973 (11.1)
Prior Heart Failure event	1 (0.0)	-	1 (0.0)
Prior atrial Fibrillation or Flutter event	16 (0.1)	-	16 (0.1)
Prior coronary event	23 (0.1)	-	23 (0.1)
Drugs n (%)			
Beta-blocker	3,839 (21.3)	67 (26.9)	3,772 (21.2)
ACEI	2,953 (16.3)	39 (15.7)	2,914 (16.4)
CCB	1,796 (9.9)	27 (10.8)	1,769 (9.9)
Diuretics	2,341 (13.0)	41 (16.5)	2,300 (12.9)
ASA	3,535 (19.6)	78 (31.3)	3,457 (19.4)
Digoxin	173 (1.0)	4 (1.6)	169 (0.9)
Nitrates	662 (3.7)	14 (5.6)	648 (3.6)
Statin	3574 (19.8)	69 (27.7)	3,505 (19.7)

ACEI, angiotensin converting enzyme inhibitor; ASA, acetylsalicylic acid; BMI, body mass index; CCB, calcium channel blocker; SD, standard deviation.

Beta-blocker use and risk of incident dementia

During 84,506 person-years follow-up, 66 BB+ patients (1.8%) and 56 BB- patients (1.5%) received a diagnosis of dementia, as shown in **Table 13**. In Cox proportional hazard models (**Table 13**), use of BB was independently associated with a two-fold increase in vascular dementia (HR:1.97; 95%CI 1.01-3.27, p= 0.046). These results were confirmed in the multivariate analysis after adjustment for incident atrial fibrillation, incident coronary event, incident stroke and incident hearth failure (HR:1.72; 95%CI 1.01-3.78, p=0.048). Conversely, treatment with BB was not associated with increased risk of all-cause, Alzheimer and mixed dementia.

Table 13. Relationship between beta blocker treatment and risk of dementia subtypes in unadjusted and multivariable-adjusted Cox regression model

Dementia subtypes	Model 1 HR (95%CI)	p-value	Model 2 HR (95%CI)	p-value
Overall Dementia	1.18 (0.83-1.69)	0.102	1.15 (0.80-1.66)	0.442
Vascular Dementia	1.97 (1.01-3.27)	0.046	1.72 (1.01-3.78)	0.048
Alzheimer Dementia	0.78 (0.44-1.40)	0.406	0.85 (0.48-1.54)	0.599
Mixed Dementia	1.18 (0.62-2.25)	0.617	1.35 (0.56-3.27)	0.501

Paper V

Patient characteristics

The study population had a mean age of 73 years, consisted predominantly of men (69%), 37% had diabetes and a high proportion of patients (87%) were considered as NYHA-class III-IV. During follow-up period, a total of 54 (23%) patients died (**Table 14**).

Table 14. Baseline characteristics of the study population

Baseline characteristic	**n=238**
Age (years; (SD))	73 (12)
Gender (female n;(%))	73 (31)
NYHA-class III-IV (n; (%))	207 (87)
Prevalent or history of smoking (n; (%))	158 (66)
BMI (kg/m^2; (SD))	28 (6)
SBP (mmHg; (SD))	140 (27)
DBP (mmHg; (SD))	81 (16)
Education level	
Elementary school, 9 years (n; (%))	125(53)
Upper secondary school, 9-12 years. (n; (%))	61(26)
College education, >12 years. (n; (%))	51(21)
Diabetes (n; (%))	87 (37)
AF (n; (%))	120 (50)
Smoking (n; (%))	158 (66)
Nt-proBNP (pmol/L; [range])	6368 [34940]
LVEF (%)	39 (16)
Death (n; (%))	54 (23)
Rehospitalization (n; (%))	136 (57)
MoCA (points; (SD))	25 (4)
MoCA<23 points (n; (%))	54 (23)
SDMT (Points)	26 (10)
TMT A (seconds; (SD))	62 (35)
AQT (seconds; (SD))	86 (26)

NYHA-class, New York heart association; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; AF, Atrial fibrillation; LVEF, Left ventricular ejection fraction; NT-proBNP, N terminal pro-atrial natriuretic peptide; MoCA, Montreal cognitive assessment; SDMT, Symbol digit modalities test; TMT A, Trail making test A; AQT, A quick test of cognitive speed

Cognitive tests associating with mortality and rehospitalization risk

In the Cox regression analysis adjusted for age and sex, continual values of all included tests yielded significant associations with an increasing risk of death. In the multivariate analysis lower score on MoCA and SDMT and longer time duration of TMT A and AQT remained significantly associated with an increased risk of death (**Table 15**).

Table 15. Cox regression analysis displaying the association between cognitive test results and risk of mortality.

Cognitive tests	HR (CI 95%)	p-value
MoCA (n=252 (61 events)) Missing, n= 0		
*Model 1**	0.74 (0.58-0.93)	0.011
*Model 2***	0.77 (0.60-0.98)	0.037
SDMT (n=244 (58 events)) Missing, n= 4		
Model 1	0.66 (0.46-0.94)	0.020
Model 2	0.68 (0.48-0.97)	0.033
TMT A (n=249 (58 events)) Missing, n=4		
Model 1	1.34 (1.08-1.65)	0.008
Model 2	1.30 (1.04-1.62)	0.020
AQT (n=247 (58 events)) Missing, n=8		
Model 1	1.35 (1.08-1.69)	0.008
Model 2	1.36 (1.07-1.71)	0.011

MoCA, Montreal cognitive assessment; SDMT, Symbol digit modalities test; TMT A, Trail making test A; AQT, A quick test of cognitive speed

* Model 1: Adjusted for gender, age

**Model 2: Adjusted for age, gender, body-mass index, systolic blood pressure, NYHA-class at admission, diabetes, educational level, prevalent atrial fibrillation and smoking

Rehospitalization risk was significantly associated with lower MoCA-score, lower SDMT-score and longer TMT A-time in the multivariate analysis (**Table 16**). When a cut-off value for MoCA was applied in the fully adjusted model, MoCA<23 was not associated with mortality, only with rehospitalization.

Table 16. Cox regression analysis displaying the association between cognitive test results and risk of rehospitalization

	Continuing values	
Cognitive tests	**HR (CI 95%)**	**p-value**
MoCA (n=251 (146 events)) Missing, n=1		
*Model 1**	0.79 (0.67-0.94)	0.007
*Model 2***	0.82 (0.68-0.98)	0.027
SDMT (n= 243 (140 events)) Missing, n= 5		
Model 1	0.75 (0.61-0.92)	0.006
Model 2	0.77 (0.62-0.95)	0.016
TMT A (n=248 (143 events)) Missing, n= 5		
Model 1	1.24 (1.06-1.46)	0.009
Model 2	1.22 (1.03-1.45)	0.020
AQT (n=246 (142 events)) Missing, n=9		
Model 1	1.14 (0.97-1.34)	0.108
Model 2	1.12 (0.95-1.32)	0.184

MoCA, Montreal cognitive assessment; SDMT, Symbol digit modalities test; TMT A, Trail making test A; AQT, A quick test of cognitive speed

* Model 1: Adjusted for gender, age

**Model 2: Adjusted for age, gender, body-mass index, systolic blood pressure, NYHA-class at admission, diabetes, educational level, prevalent atrial fibrillation and smoking

General discussion

Blood pressure and dementia risk

In **Paper I**, lower BP in advanced age, decline in BP between mid-life and advanced age and DBP decrease upon standing in midlife predicted development of all-cause dementia. In addition, sub-group analysis revealed that higher SBP and DBP in mid-life conferred to increased risk of VaD, but not combined AD and mixed dementia.

Longitudinal association between elevated blood pressure and dementia

The detrimental effect of high BP on cognitive functions was already suggested in the 1960s when air traffic controllers and pilots with elevated BP performed at a lower level on multiple measures of speed of performance[233]. Thereafter, several large observational studies have investigated the longitudinal relationship between increased BP and dementia risk and found similar associations, independent of other cardiovascular risk factors or co-morbidities [84, 88]. The lack of association between elevated BP in midlife and incident AD dementia in **Paper I** has been observed in a systematic review and meta-analysis[99]. However, the results are conflicting as increased SBP in midlife, especially in combination with high serum cholesterol has shown to increase the risk of AD dementia[101]. A possible explanation for the non-significant relationship between midlife elevated BP and AD dementia in **Paper I** might be the greater heterogenicity for AD etiology compared to VaD. Additionally, if increased BP is causally linked to incident AD dementia, antihypertensive treatment might conceal the negative effects, especially in cohorts where hypertension is more aggressively treated. This has been illustrated in a cohort study by Launer et.al., where midlife hypertension only conferred to increased risk of AD dementia in those individuals with untreated hypertension[234]. Although that we tried to adjust for use of AHT in our multivariare anlyisis in **Paper 1**, BP values at baseline examination did not confer to increased risk of AD dementia.

Hypertension may predispose VaD in several ways including an increased risk of stroke[235], cerebral microbleeds[236, 237], microvascular dysfunction due to lipohyalinosis, fibrinoid necrosis and BBB damage[88, 157, 238]. Elevated BP has also been associated with lower brain weight and increased number of beta amyloid plaques in the neocortex and hippocampus[239]. Furthermore, hypertension has been associated with subclinical or “silent” vascular brain lesions in individuals

without clinical signs of CVD[86, 240]. Hence, cognitive deficits caused by hypertension might pass unnoticed to clinicians which strengthens the importance of blood pressure control for dementia prediction. Also, hypertension has been implicated in changing cerebral autoregulation, acquiring higher perfusion pressures in hypertensive individuals in order to preserve constant cerebral blood flow (CBF)[241]. Damaging cerebrovascular effects have been shown to be mediated by the potent vasoconstrictor endothelin-1[242]. This finding is intriguing since we in **Paper II** observed that elevated plasma levels of the endothelin precursor, CT proET-1 was associated with incident VaD. In **Figure 8**, potential pathological mechanisms linking blood pressure changes to dementia risk are illustrated.

Potential methodological alterations between different reports investigating the relationship between BP and dementia must be considered in comparison of the results. Studies using self-reported hypertension as a predictor of dementia depend on the participants self-awareness which might be already affected by older age at inclusion. Moreover, BP shows a natural variation during the day and might also increase as a result of white coat hypertension[243]. In **Paper I**, the mean value of two BP measurements at rest was calculated and used in the statistical model. In ideal circumstances this measurement will represent the individuals BP level not only across hours but also days. Thus, studies using 24-hour ambulatory BP measurement probably better reflect how BP changes during the day but also reduce the effects of environmental and emotional conditions on BP levels[244].

The definition of hypertension varies between studies applying diverse BP cut-off values. In several older studies reporting midlife hypertension as an independent risk factor of incident dementia, a SBP cut-off value of $\geq$ 160 mmHg is applied which is clearly above the recommended threshold level for first grade hypertension according to the European Society of Hypertension (ESH)[84, 88, 245]. A higher threshold level for hypertension might increase the risk of overestimation of results. To overcome this methodological issue, the BP variable in **Paper I** is used as a continuous value and stratified BP-derived parameters into quartiles. Another possible cause of bias might be how the BP examinations were conducted. In MPP baseline examination, BP was measured manually compared to MPP-RES where a validated automatic sphygmomanometer was used. Another important methodological aspect is the duration of time between BP measurement and assessment of dementia diagnosis. In **Paper I**, the mean follow-up time between MPP-RES and the date of dementia diagnosis was 5 ± 1 years. Considering the rather short follow-up time between BP measurement and the diagnosis of dementia it becomes difficult to draw any conclusions whether the BP starts to decline at an earlier point of time and whether BP decline might be the result of incipient dementia. In contrast, the long-term duration between MPP baseline examination and dementia diagnosis is afflicted with the uncertainty of BP changing during the course of follow up. As exposures varies over time, so may also potential confounding factors. Prior reports focusing on midlife BP in relation to incident

dementia, the mean age span that defines "midlife" varies from 36-68 years[86]. These findings suggest that the effect of age must be considered when interpreting the longitudinal relationship between BP and dementia. Cohorts which provide measures of exposure at several age spans with a long term follow up are needed to evaluate the age effect on dementia outcome. In **Paper I**, the risk of selection bias is apparent since the survival of hypertensive subjects above 80 years old with no prior vascular event is probably not representative of most elderly patients with vascular disease. Accurate classification of dementia diagnosis is of great importance when trying to determine the impact of BP. Different classification systems have been applied in prior trials to retrieve the diagnose of dementia[88], based on extensive neuropsychological and clinical assessments. Finally, differences in confounding factors must be considered when evaluating the results in **Paper I** in comparison to previous studies. For example, in **Paper I** we did not adjust for the presence of apolipoprotein E4 which has shown to increase the risk of VaD and AD[246]. Therefore, we cannot preclude that APOE4 or other residual confounding factors did not impact the results.

Depicting the optimal blood pressure level for individuals in mid-life in order to lower the risk of future dementia has not been easy to assess. In 2018, new age-specific treatment targets for arterial hypertension were recommended by the ESC suggesting that optimal SBP and DBP for individuals below 65 years should be below 120 and 80 mmHg respectively[245]. These recommendations are based on findings in the SPRINT Research Group reporting reduced rates of fatal and nonfatal major cardiovascular events and death from any cause when lowering the SBP below 120 mmHg[149]. However, no beneficial effects on dementia incidence have been observed by treating SBP below 120 for individuals in this age category[104]. On the other hand, it has recently been shown that SBP $\geq$ 130 mmHg at age 50 increases the risk dementia later in life compared to individuals with hypertension at age 60 and 70[86]. Hence, this narrow span of SBP in relation to incident dementia is probably depending on other confounding factors such as age.
In **Paper I**, we observed a large discrepancy between the number of participants receiving AHT and prevalent hypertension. Only 7 % of the participants at baseline examination received AHT considering the large proportion (44%) of individuals with prevalent hypertension defined as SBP$\geq$140 mmHg and/or DBP$\geq$ 90 mmHg. Since AHT has shown to dampen the cognitive decline and prevent the onset of dementia, this observation might indicate that hypertension among middle-aged individuals is to a large extent untreated which might negatively impact the cognition[247].

Another important aspect is that peripheral BP is only a surrogate marker of the pulsatile energy affecting the brain which is constantly exposed to the mechanical forces of cardiac contractions. One might argue that arterial stiffness which is commonly referred to as a novel vascular risk factor is the mechanism that reflect the pulsatile force from heart to brain.

Low blood pressure within the years before dementia diagnosis

The BP reduction within the years before clinical signs of dementia observed in **Paper I** has been described previously and hypothesized as an effect of body mass index (BMI) reduction[84, 248]. Brain regions involved in BP regulation such as the brainstem and hypothalamic nuclei are affected by dementia progress[249, 250]. Furthermore, Burke and colleagues reported a strong correlation between a decrease in the number of C1 neurons in the medulla oblongata and BP dysregulation in Alzheimer patients[251]. A reversed causation has been suggested where brain lesions caused by dementia progress result in BP reduction[252]. Alternatively, a common underlying factor such as physical frailty might have contributed to progress of both CVD and dementia risk[253, 254]. BP reduction may also result in cerebral hypoperfusion which has previously been shown to precede neurodegenerative pathological changes and cognitive deficits seen in AD and VaD[255].

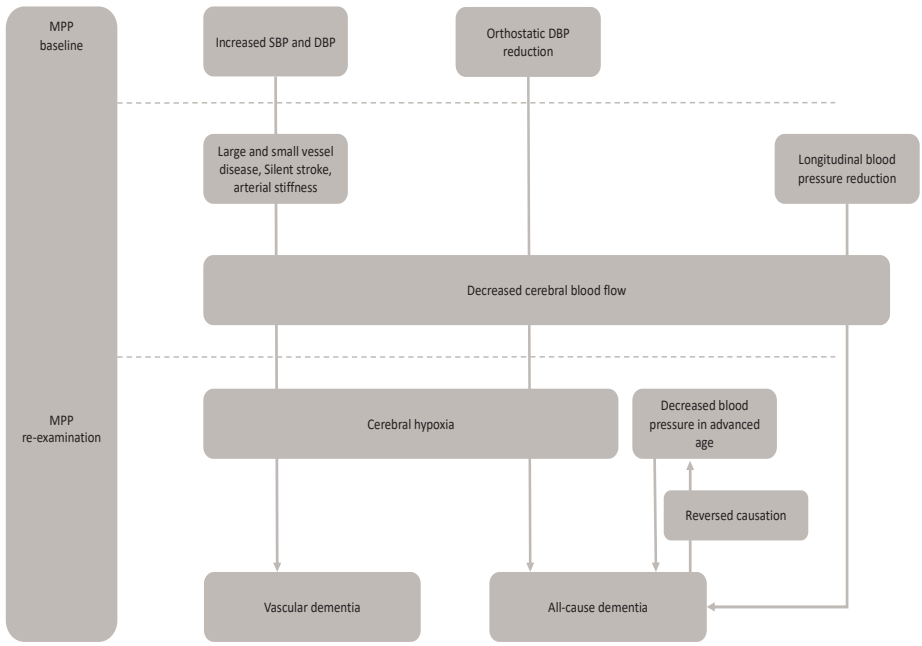
The decline of blood pressure from mid-life to older age in relation to incident dementia has been described earlier[107] where several factors probably are affecting the association. For instance, the presence of cortical atrophy and WMH in the brain have shown to be facilitated by an excessive DBP decline over 20 to 25 years[256, 257]. Additionally, cerebral autoregulation becomes impaired with advancing age as a result of decline of arterial elasticity. Between 60 to 150 mmHg of mean arterial pressure, cerebral autoregulation preserves adequate blood perfusion and flow in the brain[258]. Below 60 mmHg, cerebral autoregulation collapses and the reduction of blood flow is compensated for by enhanced oxygen extraction[259]. If the improved oxygen extraction fails to deliver enough amount of oxygen to cerebral tissues, cerebral hypoxia ensues which may result in irreversible tissue damage and development of dementia. Since no BP measurements during the course of follow-up was available, it is not possible to define when in time the BP starts to decline.

Orthostatic intolerance and incident dementia

In **Paper I**, we also aimed to investigate whether prevalent OH in mid-life yielded increased risk of dementia. Previous studies have shown that OH is a common comorbidity in individuals with dementia and a risk factor for dementia development[90]. We did not find any significant associations between prevalent OH and dementia risk which might be explained by the low prevalence of OH (383/17,493; 2.1%) among the re-examined participants compared with the original MPP cohort (6.1%)[110]. Decrease of DBP at standing in mid-life increased the risk of all-cause dementia but only in normotensive individuals. A possible explanation is that these individuals already have lower BP and therefore are more sensitive to BP drop, which might significantly reduce cerebral perfusion if the critical level is reached. The BP drop upon standing reflects an impaired autonomic function which

in absence of increased compensatory heart frequency might lead to transient cerebral hypoperfusion, contributing to repeated episodes of cerebral ischemia. The observed relationship between impaired orthostatic BP reaction and incident dementia is probably multifactorial, considering previous studies presenting OH as a marker of increased mortality and cardiovascular (CV) morbidity (coronary artery disease, heart failure, and stroke)[260, 261]. Thereby, study participants with OH at MPP baseline examination were more likely to die at younger ages, before the onset of dementia which probably is the explanation behind the lower prevalnce of OH at MPP RES compared to baseline.

Figure 8. Potential pathological mechanisms linking blood pressure changes to dementia risk



Biomarkers and dementia risk

In **Paper II**, elevated plasma concentration of MR-proANP predicted all-cause and vascular dementia while marked increase in CT-proET-1 contributed only to VaD risk. MR-proADM did not confer to dementia risk after adjustment for traditional risk factors. In **Paper III**, higher plasma concentrations of NT-proSST yielded increased risk of VaD only.

As growing evidence proposes CVD as a contributing pathology for the development of AD, the interest towards finding presumptive cardiovascular biomarkers signaling increased risk of incident AD dementia has increased[262]. The lack of association between the three cardiovascular biomarkers studied in **Paper II** and incident AD dementia was therefore to some extent discouraging. In the diagnosis of AD dementia, measurement of biochemical biomarkers in CSF including Aβ1-42, phosphorylated Tau and Total- Tau are commonly applied in clinical practice[263] whereas the use of blood based biomarkers in the diagnosis of VaD is not clinically established. The common origin of biomarkers predicting VaD in observational studies is SVD pathology involving BBB dysfunction, cerebral inflammation and breakdown of white matter myelinated fibers and extracellular matrix[48]. Biomarkers embraced as the most promising candidates in detecting VaD are elevated CSF/blood albumin ratio, altered CSF matrix metalloproteinases, CSF neurofilament and blood inflammatory cytokines and adhesion molecules[264]. Considering these observations, the selectivity of MR-proANP and CT-proET to VaD risk in **Paper II** is valuable. Therefore, the finding that plasma MR-proANP, CT-proET-1 and NT-proSST predict vascular dementia but not AD dementia adds not only a potential diagnostic tool to predict dementia development but might also provide valuable information in order to distinguish between dementia subtypes.

In **Paper II** and **III**, it is not possible do draw any conclusions regarding the potential causality between elevated levels of plasma biomarkers and dementia outcome. The biomarkers studied may only tell whether an association with dementia exists or not. If causality is warranted, Mendelian randomization studies with adequate power have to be performed. Additionally, the underlying pathophysiological role of the biomarkers in relation to incident dementia cannot be concluded since the biomarkers mediate several comorbidities associated with incident dementia. Moreover, no conclusions can be drawn whether the biomarkers possess a direct detrimental effect in the CNS. The follow-up time between assessment of the biomarkers and the time point for dementia diagnosis was relatively short. Since cognitive disorders normally progress for many years before clinical signs of dementia, the additional value of biomarker measurement within a short follow up time can be questioned. The study population in **Paper II** and **III** is composed by the surviving individuals from the baseline examination of MPP. In

this regard, a selection bias of participants enrolled for analyses might be present since the surviving individuals might be healthier.

As plasma biomarker assessment is less invasive than CSF measurement, less costly than brain amyloid imaging and more easily measured in a primary care clinic setting, it is also more practical and easily available through standard test kits. In **Paper II** and **III**, individuals with the most pronounced plasma concentrations of MR-proANP, CT-proET-1 and NT-proSST were at highest risk of dementia development suggesting that high concentration cut-off values may be used in a clinical setting to predict the development of vascular dementia. As mentioned above, the rather short follow-up time between MPP-RES and the diagnosis of dementia makes it difficult to conclude for how long period of time the biomarkers have been increased in plasma. The measurement of biochemical biomarkers is afflicted with several difficulties including timing, laboratory errors and difficulty to establish normal ranges. However, several advantages are obvious including the precision of measurement, the opportunity to establish validity and importantly the possibility to study disease mechanisms. [265].

MR-proANP

To the best of our knowledge, the findings in **Paper I** are first to describe the increased risk of VaD in relation to higher plasma concentrations of MR-proANP independent of other cardiovascular risk factors. Given the abundant relationship to CVD, the association between ANP and dementia is probably multifactorial. In a previous study by Hiltunen et al., NT-proANP did not correlate with the presence of cognitive impairment in elderly individuals[266]. Still, elevated plasma levels of MR-proANP have been shown to predict the development of AD with a sensitivity of 62.8% at a specificity of 81.1%[267]. In addition, it has been revealed that individuals with mild cognitive impairment are at higher risk of developing manifest AD if plasma concentrations of MR-proANP and MR-proADM are high[268]. Amongst individuals with mild cognitive decline, MR-proANP has been demonstrated as an important predictor of the effect of antihypertensive treatment on conversion to manifest Alzheimer dementia[269]. Protective effects of antihypertensive therapy are clearly demonstrated in younger individuals, and early initiation of a BP lowering therapy appears to be a crucial factor. Alternatively, elevated, probably compensatory, MR-proANP levels at younger age might define a subgroup of patients with marked endothelial dysfunction who would benefit most from the therapy.

Since study participants developing dementia in **Paper II** had lower blood pressure compared to individuals free from dementia, elevated plasma concentrations of MR-proANP might be viewed as a feedback mechanism to lower the blood pressure. As presented in **Paper I**, higher blood pressure levels in midlife yielded increased risk of VaD later in life. As MR-proANP is elevated in individuals with hypertension,

elevated plasma concentrations of MR-proANP might be viewed as a feedback mechanism to lower the blood pressure[270]. Perceptibly, participants developing dementia in **Paper II** had lower blood pressure compared to individuals free from dementia. Increased levels of ANP seen in individuals with incident dementia may also counteract the oxidative stress[271], which has previously been indicated as a crucial contributor for the development of vascular dementia[272].

CT-proET-1

Endothelin has been found in several areas within the brain including vascular endothelial and smooth muscle cells, macrophages and neurons[197]. In response to cerebral ischemia, ET-1 has been shown to increase the BBB permeability which is responsible for protecting the brain from unwanted molecules[273]. The level of increase has also been related to the severity of neurologic outcomes[274]. Hence, the longitudinal association between plasma levels of CT-proET-1 and VaD in **Paper III** might reflect progress of cerebral ischemia.

Another possible mechanism that could explain the association between elevated plasma levels of CT-proET-1 and incident VaD is the capacity of endothelin to stimulate proinflammatory mechanisms[275]. As vascular inflammation has been implicated in VaD pathogenesis with increased BBB permeability this might be a possible link between CT-proET and VaD[276]. Additionally, in a model of sleep apnea, exposure to chronic intermittent hypoxia stimulated release of endothelin which induced cerebral endothelial dysfunction and suppression of the cerebral blood flow via activation of endothelin type A receptors through NADPH oxidase-derived free radicals[242]. Accumulating data also suggests that ET-1 stimulates the release and potentiates the effect of other neuropeptides[275]. Hence, potential detrimental effects on cerebral tissue might be mediated by other hormones. Growing evidence suggests that amyloid β accumulation induces the release of ET-1 responsible for the reduction of CBF[277]. Also, in astrocytes surrounding the AB- plaques, a marked increase of ET-1-like immunoreactivity has been exposed[278]. Conversely, low concentration of plasma CT-proET-1 has been found in individuals with AD dementia compared to healthy control subjects. However, the ratio of MR-proANP/CT-proET-1in plasma has been outlined with predictive capacities of AD, yielding a sensitivity of 76.6% and specificity of 81.1%[267].

NT-proSST

Within the brain, somatostatin modulates neurotransmission by inhibiting the release of dopamine, serotonin and norepinephrine[201, 203]. In relation to cognitive disorders, SST has primarily been studied in AD where low concentrations have been detected in the CSF and brain tissue[279]. Furthermore, evidence has been provided that SST plays a crucial role in hippocampal and cortical

networks involved in memory and cognition enhancement[280]. By infusion of the SST selective agonist octreotide, the memory in individuals with AD improved[281]. In **Paper III**, plasma concentration of SST was not significantly associated with AD dementia risk. On the other hand, the evidence is sparse that SST is changed within plasma in AD. Interestingly, one previous study has shown that SST concentration in plasma is increased for patients with VaD compared to individuals with AD dementia[282]. Together with the finding that SST does not cross the BBB, this render the hypothesis that increased plasma concentrations of SST does not reflect the altered SST concentration within the brain. The predictive role of somatostatin in incident vascular dementia might instead be explained by its linkage to incident cardiovascular disease[208, 283] which has previously been suggested as a risk factor for VaD[276]. Hence, elevated levels of SST might reflect a general susceptibility to CVD. Since somatostatin acts as an inhibitor of other hormones, elevated levels might also reflect an effort to reduce the activity of hormones responsible for neuronal degeneration. Lastly, the assay used only targets N-terminal fragments of proSST that are present in peripheral venous blood, and thus, the paracrine effects of SST that depend on where in the body it is being secreted cannot be taken into account.

Antihypertensive treatment and dementia

Development of cognitive decline has been reported as early as one year after the diagnosis of hypertension, suggesting that early therapeutic interventions might prevent future dementia[105]. However, in randomized clinical trials investigating the use of AHT in relation to incident dementia in elderly, it has been difficult to demonstrate a protective effect[84, 284]. In a recently published randomized controlled trial by van Middelaar et al. including 1, 951 community-dwelling older individuals, use of *Calcium channel blockers* (CCBs) and *Angiotensin receptor blockers* (ARBs) were independently associated with a decreased risk of dementia[285]. Conversely, in the double-blind, placebo-controlled trial; Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG), no significant difference between treatment and placebo groups were observed[154]. This lack of association between AHT and dementia development has also been confirmed by a recent systematic review and meta-analysis independent of dementia subtype studied[286]. This appeared independent of dementia subtype. Short follow-up time, differential drop-outs, limited statistical power and less sensitive diagnostic instruments has been proposed as possible factors affecting the results[84]. Also, some trials are affected by crossover between the treatment and placebo groups, rendering a comparison between different antihypertensive agents rather than AHT vs. no AHT. Furthermore, the dementia outcome in the randomized controlled trials mentioned above was the secondary outcome as mortality due to cardiovascular risk was the main outcome.

In a smaller Swedish trial exploring the longitudinal relationship between BP reduction and dementia risk (81 dementia cases and 223 controls), Guo et al., showed that SBP reduction to 140 mm Hg or less was significantly associated with higher risk of dementia and AD compared to individuals with SBP of 140 to 179 mm Hg[287]. Further, in elderly individuals with mild cognitive deficits and AHT it has been shown that low BP rather than high is associated with reduced volumes of thalamus, putamen, and hippocampus[288]. Considering these observations together with the findings in **Paper I** that low blood pressure contributed to dementia risk, the use of AHT might exert detrimental effects on cognitive functions. In **Paper IV**, beta blockade treatment was associated with increased risk of developing vascular dementia after adjusting for traditional cardiovascular risk factors. The evidence that adverse side effects on cognition could be attributed by beta blockade treatment is sparse. However, use of first-generation beta blockers such as propranolol has been related to increased risk of fatigue[289] and reduced self-estimated sense of well-being[290]. In a study by Gliebus et al,. a trend towards worse delayed memory retrieval was observed in patients who were on CNS-active beta-blockers[291]. In a recently published article by Steinman et al,. treatment with beta blockers after acute myocardial infarction was associated with better survival but also increased risk of functional decline[292].

In **Paper IV**, no mechanistic conclusions can be drawn on how beta blockade contributes to dementia risk. However, several theories to explain these associations include both indirect effects on the cerebral hemodynamics but also direct effects mediated by the blockade of adrenergic signaling pathways in the central nervous system (CNS). Declined cardiac output caused by BB has been shown to reduce both cerebral blood flow and cerebral oxygenation[293]. Since vascular dementia occurs as a result of cerebral ischemia, the reduced cerebral oxygenation observed in individuals with beta blockade might serve as a possible explanation why beta blockade comes with higher risk of vascular dementia. Growing evidence suggests that adrenergic receptors (ADRs) located in the CNS possess important regulating abilities for cognitive and behavioral functions[294]. Noradrenaline containing neurons have proved to be highly involved in the consolidation of memory capacity through signaling in locus coeruleus and hippocampus[295]. Locus coeruleus which is the center of cells producing norepinephrine in the CNS is of great importance for many fundamental brain functions, including attention, sleep, arousal, mood regulation, learning, and memory[296]. From locus coeruleus, noradrenergic pathways are going to amygdala, hippocampus and neocortex, the foremost brain areas involved in AD[297]. Hypothetically these activities might be negatively affected by the use of lipophilic beta-blockers with the ability to cross the blood-brain barrier and bind to beta adrenergic receptors in the brain[298]. It has recently been reported that, in a rat model in which persistent long-term depression was achieved by perforant path-dentated gyrus stimulation isoproterenol, a B-ADR receptor agonist, reinforced the duration of long-term depression, a key process linked to memory processes, for over 24h[299]. In the same animal model, the

infusion of propranolol, a non-selective highly lipophilic B-ADR receptor antagonist, counteracted the positive effect of beta-adrenergic pathway in hippocampus synaptic plasticity and information processing. In addition, B_1-ADRs have been suggested as potential therapeutic targets for treatment of cognitive dysfunction in Alzheimer dementia. Involved in the regulation of neuroinflammatory processes, B_1-ADR possess neuroprotective properties.

In **Paper IV**, no information was available regarding the type of beta-blocker used. Therefore, no conclusions can be drawn whether the association between beta blocker use and dementia was driven by a "class" effect or a "molecular" effect. This aspect of concern must be noticed in review of the literature since many drugs that lower the blood pressure might have dual effects. For example, CCBs lower blood pressure by dilation of peripheral arterioles. Concurrently CCBs employ a neuroprotective effect[300]. Since AHT among patients aged 60-80 has shown lesser reduction in total mortality[301], the question has been raised whether current BP thresholds are to low and contributes to concomitant hemodynamically induced cognitive impairment. Since improvement of cognitive functions have been observed shortly afterwards the assignment to AHT, it has been questioned whether protective effects are mediated beyond the effect of lowering the blood pressure. Use of beta blockers implies a higher burden of cardiovascular disease which is the underlying pathology for vascular dementia. Therefore, the association between treatment with beta blockers and incident vascular dementia seen in **Paper IV**, might just indicate a higher prevalence of cardiovascular disease. Furthermore, increased survival due to effective AHT might conceal positive effects on cognition.

In **Paper IV** the follow-up time from beta blocker identification to dementia diagnosis was rather short. Therefore, one can assume that the VaD pathology process might have been present for several years before the final diagnosis. Hence, beta blockade treatment has probably also been administered to individuals with prevalent dementia. In a previous review article by van der Wardt et al., AHT treatment to individuals with dementia has been associated with conditions that might increase or imitate dementia including depression, orthostatic hypotension, behavioral disturbances, polypharmacy risks and interactions with cholinesterase inhibitors[302]. Another important aspect when evaluating the effect of AHT on cognition and dementia risk is the growing evidence suggesting that genetic and physiologic factors might modulate the effect of BP treatment on cognitive outcomes. For example, the presence of APOE ε4 allele and hypertension has been linked to steeper cognitive decline over a 21-year period[303]. Hence, the assessment of APOE4 genotype might foretell which individuals who might benefit in cognitive function from treatment with AHT.

Heart failure and cognitive decline

In **Paper V,** four cognitive tests assessing global cognitive function, cognitive speed, attention and task switching predict post-discharge mortality in patients hospitalized due to heart failure, independently of traditional risk factors. Moreover, lower performance in three cognitive tests heralds increased risk of re-hospitalization in heart failure patients. These findings confirm data from previous studies suggesting cognitive function as a risk marker of mortality and rehospitalization in HF patients[139, 141, 304]. In **Paper V**, the prevalence of cognitive decline according to a MoCA score below 23 among HF patients was 23 %. In prior reports in subjects with HF, cognitive decline has been detected in 25 to 75 % [304, 305]. This wide range of prevalence might be attributed to difference in study populations including age, sample size and HF severity. Additionally, different cognitive tests have been applied to assess cognitive function and different criteria in diagnosing HF have been practiced[137].

Several theories have been proposed to explain the underlying pathophysiology of cognitive impairment and dementia in HF patients. In a recently published position paper by the European Journal of Heart Failure, the authors propose a systematic approach based pathophysiological principles to better understand the interactions between the heart and the brain[304]. *First*, heart failure represents a major risk factor for the incidence of ischemic stroke due to thrombosis. Left ventricular dysfunction leads to increased ventricular volume in end diastole which stimulates blood stasis in the left ventricle and the left atrium, promoting the development of intracardiac thrombosis and the risk of embolic stroke[306]. Moreover, the stroke risk in HF is driven by the stimulation of hypercoagulability facilitated by reduced fibrinolysis, endothelial dysfunction, inflammatory activation and malfunctioning of cerebral autoregulation[304]. In the Framingham Heart study, the relative risk of stroke in male HF patients was 4.1 times higher than in individuals without HF[307] . The occurrence of cerebral stroke may cause direct neurologic deficits or remain clinically unnoticeable, so called “silent”, which is common in HF[308]. Also, the presence of silent infarctions has been closely associated with cognitive function and dementia[309].

Secondly, cerebral blood flow (CBF) in HF patients has been shown to be chronically reduced which has previously been depicted as an important contributor for cognitive decline and dementia[310]. The reduction of CBF has also been shown to aggravate in HF patients during exercise compared to healthy individuals suggesting that HF patients are unable to remain normal cerebral hemodynamic responses during orthostatic stress[311]. In patients with cardiac transplantation or cardiac resynchronization therapy, the following improvement of CBF might also improve cognitive function[311]. The maintenance of CBF is accomplished by complex multiple overlapping regulatory mechanisms which can be divided in to

three major mechanistic groups: global metabolic, neurogenic and pressure autoregulation[312]. In case of reduced mean arterial pressure (MAP), the cerebral autoregulation stimulates cerebral arteries to dilate in order to maintain constant CBF. When MAP falls below 60 mm Hg, the cerebral autoregulation is unable to maintain constant flow and cerebral hypoperfusion and ischemia ensues[312]. Hence, decreased cardiac output (CO) and SBP in HF might result in cerebral hypoperfusion responsible for the neuroanatomic and neuropsychological changes. Subcortical regions of the brain including the periventricular white matter, basal ganglia, and hippocampus are particularly susceptible to ischemic lesions due to their circulatory blood supply. In HF patients with low CO these areas become hypoperfused and prone to ischemia[152]. Optimal HF treatment has shown to restore CBF to normal levels and thereby decrease the presence of WML commonly seen in HF patients[313]. Finally, the cognitive decline observed in HF patients might also be a result of other HF comorbidities such as sleep apnea, anemia, vitamin deficiency, renal failure and depression[138].

The detection of cognitive impairment among elderly patients in general hospital settings is low[314, 315]. The underestimation of prevalent cognitive decline has also been observed in primary care[316, 317]. As cognitive impairment has been linked to increased risk of mortality but also conversion to dementia, the need for cognitive screening has been suggested. A diagnostic approach to heart failure induced cognitive impairment has been proposed including screening for impaired memory and executive functions, as well as anatomic brain changes (WMH; medial temporal atrophy; frontal lobe and hippocampal atrophy), elevated levels of IL-6; TNF-a; cortisol; and epinephrine[138]. In the European society of Cardiology (ESC) guidelines for the treatment of heart failure, it is recommended that support from a multidisciplinary HF team in collaboration with specialist dementia support teams, alongside medication compliance aids, tailored self-care advice and involvement of family and caregivers, may improve adherence with complex HF medication and self-care regimens[125]. Physical training programs and nurse-based memory interventions in a setting of integrated HF care have been suggested as possible non-pharmacological ways to prevent cognitive decline in HF patients[318, 319]. Therefore, we acknowledge the importance to detect and treat cognitive deficits in HF patients, not only to improve their quality of life but also in order to decrease the mortality and to avoid readmission.

Cognitive tests were performed in older patients who were under treatment for acute HF. In the setting of acute HF, some patients experience delirium which is a reversible condition of confusion. Hence, cognitive test results in **Paper V** might be influenced by this condition and not from chronic cognitive impairment or dementia. Cognitive tests results are biased by several confounding factors including language ability, education level, visual and hearing perception. Additionally, test results might be influenced by interindividual differences in cognitive compensatory mechanisms called the cognitive reserve[35, 320]. In **Paper**

V, the readmission rate was 57 % which is higher compared to another study reporting a 3 months months-readmission rate of 40 % due to cardiac causes [321]. A possible explanation might be that patients were retrieved from a heart failure clinic which probably represent a population with more severe HF symptomatology.

Future perspectives

In 2015, the estimated number of individuals suffering from dementia worldwide was 47 million but due to the large increase in life expectancy and absence of disease modifying treatment, the prevalence of dementia is expected to reach 131 million by year 2050[26]. In order to effectively meet the expected expansion of dementia cases on a global level, the G8 health ministers declared in the 2013 summit the ambition to identify a disease-modifying treatment for dementia by 2025 and to increase the amount of funding for dementia research to reach that goal [322]. To deliver and co-ordinate this plan of action, the World Dementia Council (WDC) was created. In December 2018, five years after the agreement, the WDC hosted a second summit where steps towards finding better diagnostic biomarkers and new strategies in the care of dementia were acknowledged. However, no curative treatment is available today despite the conduction of numerous treatment trials.

To this concern, the surge of finding ways to effectively prevent the outcome of cognitive decline and dementia has evolved. Preventive actions are supported by findings in observational studies including western population cohorts where dementia incidence has decreased[25, 323]. The reduction has been suggested as a result of improved education and reduction of vascular risk factors. Bearing in mind that approximately 30 % of all dementia cases worldwide have been suggested to be attributed by modifiable risk factors it becomes clear that detecting risk factors for dementia development is essential[324]. Although several observational studies have indicated promising results for risk factor reduction in relation to decline of incident dementia, results from single and multidomain clinical trials do not provide conclusive evidence that risk factor treatment leads to lower dementia incidence[325]. In this aspect, the intention of this thesis has been to further investigate whether particular risk factors or biomarkers might contribute to the understanding why some individuals are more susceptible to develop cognitive impairment or dementia. In spite of the fact that no causality can be drawn from our results, the included papers provide insights how factors signaling vascular risk might acts as markers of increased dementia risk.

This thesis leaves many questions unanswered, not at least the pathophysiological reason why BP changes, vasoactive and endocrine biomarkers studied in **Paper I** to **III** are linked with increased risk of dementia. To further investigate the underlying mechanisms behind these findings, our research group is currently performing an animal study in which the impact of induced hypertension on cerebral vasculature

and cognition in mice is examined. Twenty-four mice have been categorized into three equally sized groups; (1) No hypertension, (2) Induced hypertension for 6 months, (3) Induced hypertension for 12 months. To investigate the cerebral adaptations upon blood pressure normalization, a group of mice will be maintained hypertensive for 6 months and then allowed to recover for another 6 months and compared to one group that is hypertensive for 12 months together with a normotensive control group. Mice in this study will go through a magnetic resonance of the brain (MR) session at baseline, 6 months and 12 months. Immediately after the MR session, before recovery from anesthesia, blood samples will be collected for metabolomics/proteomics and biomarker analysis (e.g. **ET-1** and **ANP**). Behavior tests and blood pressure measurements will be performed in the days prior the MR scans. The last behavior test battery will include a novel object recognition test and a novel object location test, in addition to the open field and Y-maze tests.

In **Paper V**, the risk of rehospitalization and mortality in relation to cognitive test results in heart failure (HF) patients was addressed. With the aim to explore cerebral hemodynamics in HF patients in regard to cognitive performance, we are currently investigating whether the presence of HF affects cerebral tissue oxygenation relative to changes in hemodynamic parameters during controlled orthostatic stress. Preliminary results including 61 patients with HF (mean-age: 71±11 years, 82% male, NYHA class I–III) from the HARVEST cohort and in 60 non-HF control individuals (mean age: 60±12 years, 42% male), lower cerebral saturation after 10 minutes of active standing was independently associated with HF. We are currently aiming to investigate whether cognitive test results are correlated with cerebral oxygenation.

A possible theory why cognitive impairment in HF patients included in **Paper V** yielded increased risk of rehospitalization might be due to reduced compliance of prescribed drugs. To further examine this, we are planning to randomize HF patients to cognitive testing or not at discharge and give support to patients with low cognitive scores and actively ensure drug compliance in these subjects. Outcomes would be rehospitalization and mortality rates compared between the two groups.

Finally, as this thesis is coming to an end, I would like to call for wider collaborations in dementia research reflecting its multimodal nature demanding multitarget interventions from primary care to specialist medical regimens. As a resident physician in Cardiology I am frequently involved in clinical situations where the heart has exerted negatively effects on other organs recognized as the cardiorenal and cardiohepatic syndromes. I hope that this thesis adds insights with regards to the relationship between cardiovascular factors such as BP levels, vasoactive BMs, HF, beta blockade with cerebral function.

Summary in Swedish

Demens är ett samlingsbegrepp för sjukdomar som drabbar hjärnan och som leder till permanent nedsättning av kognitiva funktioner såsom minne, mental snabbhet, exekutiva funktioner och språk [326]. Nedsatt kognitiv funktion och utveckling av demenssjukdom får stora konsekvenser för individen och närstående men även för samhället inkluderande stora kostnader för vård och omsorg av patienter med demenssjukdom[327, 328]. Med ökad ålder sker en exponentiell ökning av antalet demensfall som år 2015 beräknades till 57 miljoner globalt sett, en siffra som förväntas att stiga till 135 miljoner år 2050 [329]. Denna förväntade ökning synliggör ett stort behov av att finna nya mål för prediktion och prevention av demenssjukdom. Huvudsyftet med rådande avhandling har därför varit att undersöka sambandet mellan kardiovaskulära riskfaktorer (blodtrycksnivå, ortostatisk hypotension, blodtryckssänkande medicin) samt vasoaktiva biomarkörer med risken för att utveckla demens. Därutöver har vi studerat huruvida kognitiva test kan användas för att prediktera mortalitet samt återinläggning för patienter med hjärtsvikt.

Delprojekt I

Tidigare studier har visat samband mellan högt blodtryck i medelåldern och utveckling av demens senare i livet [84, 330]. Parallellt har man kunnat visa att ortostatisk hypotoni (blodtrycksfall från liggande till stående position) (OH) samt symtom på ortostatisk intolerans såsom yrsel och suddig syn predikterar nedsättning av kognitiva funktioner [113]. Försämring av ortostatisk blodtryckskontroll är ofta associerat till ökat blodtryck och antihypertensiv behandling [110] medan lågt habituellt blodtryck ökar risken för försämrat blodflöde i hjärnan[114]. Vår forskargrupp har undersökt hur blodtrycksskillnader över tid relaterar till framtida demens. För att uppnå detta begärdes information ut om demensdiagnos i Patientregistret fram till 31/12-2009 för individer inkluderade i den prospektiva studien Malmö förebyggande medicin (MFM) återundersökning (n=18,240). Det som begärdes ut var demensdiagnoser registrerade efter baslinjeundersökningen i MFM (1974-1992) där 471 individer hade demensdiagnos registrerad i Patientregistret. Av dessa individer bedömdes 428 ha en validerad demensdiagnos; 142 Alzheimers sjukdom, 96 Vaskulär demens, 114 Blanddemens, 38 Lewy body-demens/Parkinson demens, 4 Frontotemporal demens, 34 fall av ospecifik demens. Av dessa 428 validerade demensfall hade 54 personer en demensdiagnos före

återbesöket i MFM (prevalent demens vid återundersökningen: 2002-2006), och 374 fick en demensdiagnos mellan återbesöket i MFM och 31/12 2009 (incident demens). I multivariata regressionsanalyser justerade för traditionella riskfaktorer fann vi att en minskning av det diastoliska blodtrycket vid uppresning i medelåldern; en minskning av blodtrycket mellan medelålder och äldre ålder samt att lägre blodtryck i ökad ålder alla var oberoende riskfaktorer för utveckling av demens. Därutöver fann vi att ökade blodtrycksnivåer i medelåldern var associerade med ökad risk att utveckla vaskulär demens senare i livet.

Delprojekt II

I en publicerad studie (*J. Intern Med. 2017. Apr 13*) [331] kunde vår forskningsgrupp påvisa ett longitudinellt samband mellan blodtrycksreglerande biomarkörer och incident demens. De tre biomarkörer som studerades var atrial naturistisk peptid (ANP), endothelin-1 (ET-1) och adrenomedullin (ADM) vilka alla i tidigare studier visat sig vara förknippade med reglering av blodtrycket men även förekomst av arterioskleros [332, 333]. Eftersom bioaktiva peptider är mycket svårmätbara användes nyligen utvecklade mer känsliga och stabila metoder för att detektera deras prekursor fragment, dvs. midregional pro- atrial natriuretic peptide (MR-proANP), C-terminal endothelin-1 precursor (CT-pro ET1) och midregional proadrenomedullin (MR-proADM). Förhöjda nivåer av CT-proET-1 har associerats med högre incidens av hjärtsvikt samt hjärtinfarkt [334, 335], medan ökade plasmanivåer av MR-proADM and MR-proANP observerats vid hypertoni [183, 336, 337]. I tvärsnittsstudier har det även rapporterats att plasma MR-proANP och MR-proADM är förhöjda vid Alzheimer demens [267, 277]. Vår hypotes var att dessa peptider som visats vara viktiga faktorer för reglering av blodtrycket samt utvecklig av endoteldysfunktion kunde prediktera utvecklingen av demens. För att undersöka detta använde vi data från den prospektiva studien MFM återundersökning där 5, 347 individer (män, 70%; ålder, 69 ± 6 år) utan fastställd demensdiagnos screenades för plasma MR-proANP, CT-proET-1 och MR-proADM. Under en uppföljningstid på 4,6 år diagnosticerades 373 patienter (7 %) med demens (120 Alzheimers demens, 83 vaskulär, 102 blanddemens, och 68 annan etiologi). Sambanden mellan plasmanivån av biomarkörerna vid baslinjeundersökningen och demens testades med multivariata regressionsanalyser justerade för traditionella riskfaktorer. Vi fann att ökade plasmanivåer av MR-proANP var en oberoende prediktor för demens i stort och även vaskulär demens samt att ökade nivåer av CT-proET- 1 indikerade högre risk för vaskulär demens.

Delprojekt III

I utvecklade länder tillhör Alzheimer, - samt Vaskulär demens de vanligaste demensformerna och tillsammans utgör de mer än 80 % av rapporterade fall [338]. Eftersom vaskulär samsjuklighet är vanligt förekommande vid Alzheimer demens är diagnosticeringen inte bara svår utan även utmanande då de 2 demenstyperna kan finnas i kombination eller med andra neurodegenerativa sjukdomar [339]. Denna överlappning benämns ofta som blanddemens. I avsikt att särskilja de olika demenstyperna från varandra har biomarkörer förslagits som diagnostiska verktyg, däribland α-synuclein, amyloid-beta peptider och tau protein [340]. Upptäckt av nya biomarkörer kan möjliggöra att man tidigare kan identifiera individer med ökad risk för att utveckla demens. Eftersom olika kardiovaskulära riskfaktorer däribland hypertoni, rökning, hyperlipidemi samt prevalent kardiovaskulär sjukdom alla har associerats med utveckling av demens, har intresset för att finna kardiovaskulära biomarkörer med potential att prediktera demens ökat under senare år. Somatostatin (SST) som är en peptid med stor spridning inom det centrala nervsystemet (CNS) har som övergripande funktion att inhibera frisättning andra hormon däribland thyroidea stimulerande hormon (TSH), insulin, serotonin m.fl. [201, 203]. Därutöver har det rapporterats att patienter med prevalent vaskulär demens har ökade nivåer av SST i plasma [341]. Eftersom plasma SST också har associerats med utveckling av kardiovaskulär sjukdom hade vi som hypotes att förhöjda nivåer även bör prediktera utveckling av demens, och då speciellt vaskulär demens [208]. För att testa denna hypotes har vi, för individer inkluderade i MFM återundersökning (n=5, 347), analyserat huruvida plasmanivåer av det stabila prekursor fragmentet N-terminal prosomatostatin (NT-proSST) är longitudinellt associerat till utveckling av demens hos äldre individer. Vi fann att förhöjda nivåer av NT-proSST i plasma predikterade utveckling av vaskulär demens.

Delprojekt IV

Vi har i **delprojekt 1** kunnat visa en minskning av blodtrycket mellan medelålder och äldre ålder samt att lägre blodtryck i ökad ålder alla är oberoende riskfaktorer för utveckling av demens. I **delprojekt 2** har vi även visat på ett longitudinellt samband mellan blodtrycksreglerande biomarkörer och incident demens. I delprojekt 4 har vi valt att studera huruvida risken för att utveckla demens påverkas om man behandlas med betablockad som är ett blodtryckssänkande läkemedel. Tidigare studier har visat att behandling med betablockerare ökar risken för att för att utveckla nedsatt kognitiv funktion[165]. Däremot finns inga tidigare studier som longitudinellt utforskar sambandet mellan behandling med betablockad och risken för demensutveckling. För att undersöka detta har vi i den prospektiva studien MFM återundersökning begärt ut från svenska patientregistret data för demensdiagnos. 18,063 individer (medelålder 68.2, män 63.4%) inkluderades och följdes över 84,506 person-år. Patienter med prevalent cerebrovaskulär sjukdom och demens

exkluderades. För att undersöka hur betablockad påverkade risken för demens, jämfördes 3,720 matchade par av dem som hade och inte hade beta-blockad vid baslinjeundersökningen. Totalt utvecklade 122 (1,6%) individer demens under uppföljningsperioden. I multivariata regressionsanalyser såg vi att användning av beta-blockad associerades med ökad risk för att utveckla vaskulär demens. Detta samband kunde ej observeras för dem med Alzheimer demens eller för dem med blanddemens.

Delprojekt V

I delprojekt 5 har vi valt att studera huruvida kognitiva test kan användas för att utvärdera risken för mortalitet samt återinläggning för patienter med hjärtsvikt.

Inom slutenvården i Sverige behandlas varje år 22 000 personer för hjärtsvikt. Syftet med behandlingen är att hjärtat skall orka pumpa ut tillräcklig mängd blod och därmed tillgodose kroppens syrebehov. Uppemot 2 % av Sveriges befolkning, d.v.s. 200 000 människor uppskattas lida av symptomgivande hjärtsvikt och lika stor mängd tros lida av latent, d.v.s. icke-symptom givande hjärtsvikt. Trots att hjärtsviktsbehandlingen genomgått stora förbättringar under de senaste decennierna kvarstår faktum att antalet människor som dör av hjärtsvikt varje år överstiger antalet som dör av cancer[342] och den årliga kostnaden för behandling och hospitalisering i Sverige uppgår till över 2 procent av hela sjukvårdsbudgeten[343]. Antalet hjärtsviktspatienter förväntas stiga markant eftersom befolkningen blir allt äldre samt att allt fler överlever hjärtinfarkt som är en av de vanligaste orsakerna till hjärtsvikt[344]. Den ökande andelen äldre i samhället bidrar inte bara till ökad prevalens av hjärtsvikt, utan även till ökat antal individer med nedsatt kognitiv förmåga.

För att undersöka om resultat på kognitiva test predikterar mortalitet och risk för återinläggning för hjärtsviktspatienter har vi använt oss av data från den pågående studien HARVEST (HeARt and brain failure InVESTigation study). HARVEST har som syfte att systematiskt studera sambandet mellan hjärtsvikt, kognition och patologiska förändringar i hjärnan hos hjärtsviktspatienter. 238 patienter som vårdats inneliggande för hjärtsvikt i Malmö hade data för följande kognitiva test; Montreal Cognitive Assessment (MoCA), A Quick Cognitive test (AQT), Trail making A (TMT A) och symbol digit test modalities test (SDMT). I multivariata regressionsanalyser justerade för traditionella riskfaktorer fann vi att lägre resultat för MoCA och SDMT samt längre tidförbrukning för TMT A och AQT predikterade mortalitet. Nedsatta resultat gällande MoCA, AQT och TMT A var även signifikant associerade med ökad risk för återinläggning.

Errata

Paper I

In Table 4, the number of individuals with AD and mixed dementia should be 256.

In the discussion section, the cerebral perfusion pressure is stated to be preserved between 60 and 160 mmhg of systemic SBP. Systemic SBP should be omitted and corrected to mean arterial pressure (MAP).

Reference 2 in the introduction refers to the longitudinal relationship between high BP in midlife and cognitive decline, not dementia which is printed in the manuscript. It should be omitted and replaced with reference 31.

Reference 25 presents the cross-sectional relationship between low SBP and DBP with dementia, not with incident dementia which is stated in the discussion.

Reference 33 should be omitted and replaced with; Turin, T.C., et al., *Hypertension and lifetime risk of stroke.* J Hypertens, 2016. **34**(1): p. 116-22.

Paper II

In the introduction, reference 4 refers to findings that the listed CVD risk factors have been associated with increased risk of dementia death later in life, not incident dementia.

In the introduction, reference 8 should be omitted and replaced with reference 7.

Reference 9 refers to findings that elevated levels of plasma ET-1 are associated with increased long-term mortality in a high-risk STEMI population, not with incident myocardial infarction.

Reference 12 should be omitted and replaced with; Gegenhuber, A., et al.,*Comparativeevaluation of B-type natriuretic peptide, mid-regional pro-A-type natriuretic peptide, mid regional pro-adrenomedullin, and Copeptin to predict 1 year mortality in patients with acute destabilized heart failure.* J Card Fail, 2007. **13**(1): p. 42-9.

In the introduction, it should be corrected that prevalent AD has only been associated with increased levels of MR-proANP and MR-proADM.

In the discussion, reference 13 should be omitted and replaced with; Shah, R., *Endothelins in health and disease.* Eur J Intern Med, 2007. **18**(4): p. 272-82.

Paper III

Reference 11 in the introduction should be omitted and replaced with reference 22.

Reference 30 should be omitted.

In paper II and III, the correct number of prevalent dementia diagnoses are 54, missing values 17 and validated diagnoses 427.

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