Association of novel vascular risk markers with cognitive function and dementia: special focus on arterial stiffness

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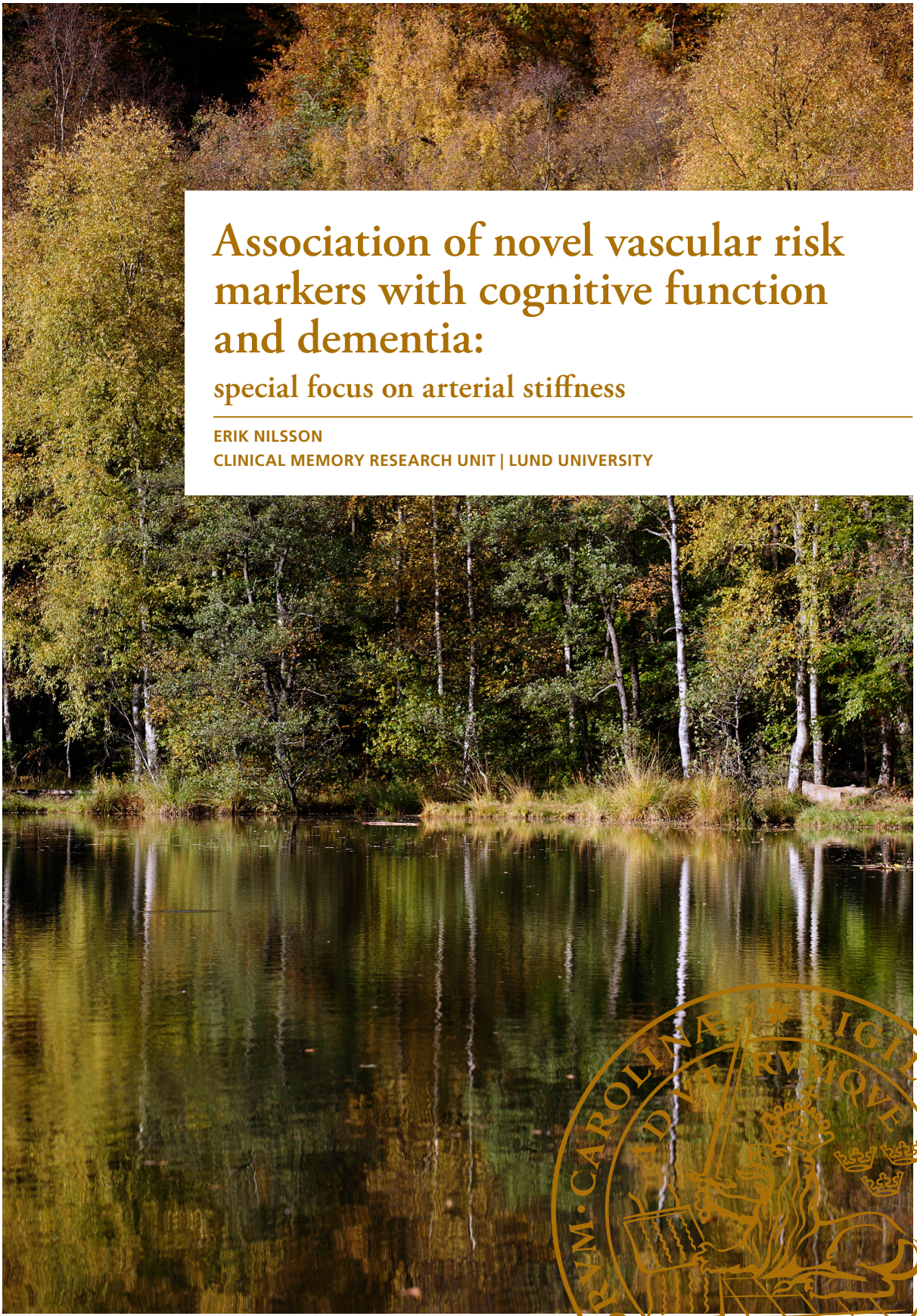

Association of novel vascular risk markers with cognitive function and dementia:

special focus on arterial stiffness

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LUND
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Carotid-femoral pulse wave velocity (c-f PWV), a marker of arterial stiffness, has been suggested to reflect the cumulative damage of known and unknown risk factors on the arterial wall over a long period of time. In **Paper I** (n = 2637, mean age 72.1 years), higher c-f PWV was cross-sectionally associated with worse results on AQT, a test of cognitive speed. The association was non-linear, and it could be explained by the individuals in the top decile of c-f PWV.

In **Paper II** (n = 2548, mean age 72.1 years at follow-up), blood pressure (BP) was inversely associated with cognitive function cross-sectionally, but not prospectively with BP measured 17 years before cognitive testing. Central (aortic) BP did not show a stronger association with the cognitive outcome than brachial BP.

Copeptin is considered a reliable surrogate marker for the neurohypophyseal hormone vasopressin. In **Paper III** (n = 18 240, mean age 69.3 years), baseline plasma copeptin level predicted incident vascular dementia during 4.2 years of follow-up, but it did not predict incident Alzheimer's disease or all-cause dementia.

In **Paper IV** (n = 3056, mean age 72.1 years), baseline c-f PWV was not associated with prevalent dementia, and it did not predict incident dementia during 4.6 years of follow-up. Thus, c-f PWV has repeatedly been associated with cognitive test results and markers of cerebral small-vessel disease in large population-based studies, but not with dementia risk.

Lower baseline levels of some of the 'traditional' cardiovascular risk factors (hypertension, hypercholesterolemia, obesity) were associated with an increased risk of dementia during follow-up in Papers III and IV. This highlights that new vascular risk markers are needed in elderly patients, and the observational research presented in this thesis provides insights about some of these new markers.

Key words: Alzheimer's disease, AQT, arterial stiffness, blood pressure, cognition, copeptin, dementia, epidemiology, MMSE, pulse wave velocity, vascular dementia

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To Sophie, Elise, Oskar, and Signe

”If the only tool you have is a hammer, you tend to see every problem as a nail”

Abraham Maslow (1908-1970)

Contents

Abstract

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Populärvetenskaplig sammanfattning på svenska

Ordet kognition betyder ungefär ”tankeförmåga” och innefattar bl.a. minne, uppmärksamhet och språkliga funktioner. Den kognitiva förmågan försämras hos alla människor som en del i det normala åldrandet. När den kognitiva svikten är så uttalad att vardagen blir påverkad talar man om demens, ett tillstånd som ökar exponentiellt med åldern. Med tanke på att befolkningsutvecklingen i Sverige och världen leder till att allt fler blir allt äldre, beräknas antalet dementa öka kraftigt framöver. Den vanligaste anledningen till demens är Alzheimers sjukdom och den näst vanligaste är så kallad vaskulär demens, d.v.s. demens orsakad av kärlförändringar. Det har länge varit känt att faktorer som leder till hjärt-kärlsjukdom (högt blodtryck, övervikt, diabetes, högt kolesterol etc.) kan leda till vaskulär demens, men under senare tid har det framkommit att dessa faktorer möjligtvis också kan orsaka eller bidra till Alzheimers sjukdom. Vidare har det framkommit att sambandet mellan dessa så kallade ”traditionella” hjärt-kärlriskfaktorer och kognitiv funktion och demens är ytterst komplext. Exempelvis har man funnit att närvaro av dessa riskfaktorer i medelåldern verkar öka risken för demens i åldrandet, men att närvaro av dem hos äldre personer inte alls verkar öka risken på samma sätt. Klart är därför att det finns ett behov av att hitta nya markörer som bättre speglar hjärt-kärlrisken över hela livet. Detta för att:

a) förstå mer om mekanismerna bakom uppkomsten av kognitiv svikt och demens

b) korrekt kunna värdera risken för framtida demens hos en person

c) korrekt kunna diagnosticera vilken typ av demens en patient har

d) vägleda prevention och behandling.

Olika mått på kärlstelhet skulle kunna utgöra sådana nya markörer. Till följd av åldrande, högt blodtryck och många andra faktorer blir stora kroppspulsådern (aorta) stelare med åldern. Eftersom ett stelt rör leder en pulsvåg snabbare än ett elastiskt rör är pulsvågshastigheten (hastigheten på pulsvågen som varje hjärtslag skapar) i aorta ett mått på kärlstelheten. Ett annat tecken på kärlstelhet är om blodtrycket i aorta är nästan lika högt som blodtrycket i armen.

Ytterligare en intressant ny markör för hjärt-kärlrisk är ämnet copeptin, som kan mätas i ett blodprov och som speglar nivåerna av hormonet vasopressin i blodet. Vasopressin är mest känt för att det reglerar salt- och vätskebalansen i kroppen, men det har även många andra funktioner.

Denna avhandlings syfte var att studera sambanden mellan nya markörer för hjärt-kärlrisk (pulsvågshastighet, blodtryck i aorta, copeptin) och kognitiv funktion och demens. Vi använde oss av data insamlade i två stora befolkningsstudier: Malmö Förebyggande Medicin och Malmö Kost Cancer.

I **delarbete I** undersökte vi sambandet mellan pulsvågshasighet och resultat på kognitiva tester. Det visade sig att individer med stelare kärl presterade sämre fr.a. på ett test som mäter snabbhet och uppmärksamhet. Denna effekt kvarstod efter att vi statistiskt justerat för de traditionella hjärt-kärlriskfaktorerna, vilket kan tolkas som att information om pulsvågshastighet är intressant även när man känner till värdena på de traditionella hjärt-kärlriskfaktorerna.

Flera tidigare studier har funnit att högre blodtryck är associerat med sämre resultat på kognitiva tester. Eftersom blodet förs till hjärnan från aorta och inte från armen, ville vi i **delarbete II** undersöka om blodtryck i aorta var starkare kopplat till kognition än vad blodtryck i armen var. Vi fann att högre blodtryck mycket riktigt var associerat med sämre resultat på kognitiva tester, men att denna effekt inte var starkare för blodtryck i aorta än för blodtryck i armen.

Delarbete III undersökte om copeptin uppmätt på icke-dementa individer kunde förutsäga insjuknande i demens. Vi fann att de som insjuknade i vaskulär demens under 4,2 års uppföljning uppvisade högre copeptin vid baslinjen, men att så inte var fallet för Alzheimers sjukdom. Fyndet att copeptin är selektivt associerat med vaskulär demens är intressant men måste upprepas av andra forskargrupper innan säkrare slutsatser kan dras.

I **delarbete IV** återknöt vi till fynden i delarbete I, men nu studerade vi demensrisk i stället för kognitiva testresultat. Vi fann inget samband mellan pulsvågshastighet och risk för att utveckla demens under 4,6 års uppföljning, och de som redan hade en demenssjukdom vid baslinjen hade inte högre pulsvågshastighet än övriga. Våra fynd är överlag överensstämmande med de som hittats i andra befolkningsstudier. Således verkar det som att individer med stelare kärl har en något sämre kognitiv förmåga (i genomsnitt), men att de inte har en markant ökad risk att utveckla demens i allmänhet. I avhandlingens diskussionsdel spekuleras kring varför det förhåller sig så. Det kan exempelvis finnas statistiska förklaringar (att antalet demensfall är för litet för att upptäcka sambandet). Det kan också vara så att stela kärl speglar en generell åldrandeprocess som hänger samman med en något ökad åldersrelaterad kognitiv nedgång, men som kanske inte hänger så starkt samman med demens - som ju snarare är en sjukdom i hjärnan än ett uttryck för åldrande.

Avslutningsvis kan det noteras att många av de traditionella hjärt-kärlriskfaktorerna uppvisade omvända (inversa) samband med demensrisk. Med andra ord var det *lägre* blodtryck, *lägre* vikt och *lägre* kolesterol som var associerade med en *högre* risk för demens under uppföljningstiden. Detta kan eventuellt förklaras av att vi hade en så pass kort uppföljningstid att demens-förändringarna i hjärnan redan hade börjat vid baslinjen, även om individen då inte var dement. Det är välkänt att dessa förändringar i hjärnan kan medföra att nivån på de traditionella hjärt-kärlriskfaktorerna sjunker, och möjligen är det detta som förklarar sambanden. I vilket fall pekar fynden på att den komplexa relationen mellan hjärt-kärlriskfaktorer och demens behöver belysas mer ingående framöver.

List of original papers

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals:

I. **Nilsson ED**, Elmståhl S, Minthon L, Nilsson PM, Pihlsgård M, Tufvesson E, Nägga K. Nonlinear association between pulse wave velocity and cognitive function: a population-based study. J Hypertens. 2014;32(11):2152-2157.

II. **Nilsson ED**, Elmståhl S, Minthon L, Nilsson PM, Pihlsgård M, Nägga K. Associations of central and brachial blood pressure with cognitive function: a population-based study. J Hum Hypertens. 2016;30(2):95-99.

III. **Nilsson ED**, Melander O, Elmståhl S, Lethagen E, Minthon L, Pihlsgård M, Nägga K. Copeptin, a marker of vasopressin, predicts vascular dementia but not Alzheimer's disease. J Alzheimers Dis. 2016;52(3):1047-1053.

IV. **Nilsson ED**, Elmståhl S, Minthon L, Pihlsgård M, Nilsson PM, Hansson O, Nägga K. No independent association between pulse wave velocity and dementia: a population-based, prospective study. J Hypertens. 2017 doi: 10.1097/HJH.0000000000001480. Jul 12 Epub ahead of print.

Abbreviations

ABI	ankle-brachial index
AD	Alzheimer's disease
AQT	a quick test of cognitive speed
b-a PWV	brachial-ankle pulse wave velocity
BMI	body mass index
BP	blood pressure
c-f PWV	carotid-femoral pulse wave velocity
CI	confidence interval
cIMT	carotid-intima media thickness
CV	cardiovascular
CVD	cardiovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
EVA	early vascular ageing
HDL	high density lipoprotein
HR	hazard ratio
ICD	International Classification of Diseases
LDL	low density lipoprotein
MAP	mean arterial pressure
MCI	mild cognitive impairment
MDC	Malmö Diet and Cancer study
MDC-CV	Cardiovascular Arm of MDC
MMSE	Mini-Mental State Examination
MPP	Malmö Preventive Project
OR	odds ratio
PP	pulse pressure
SD	standard deviation
SNPR	Swedish National Patient Register
TOD	target organ damage
VaD	vascular dementia
VCI	vascular cognitive impairment
WMH	white matter hyperintensities

1 Introduction

1.1 An ageing population

The prevalence of dementia increases exponentially with age, and is around 1% worldwide in the age group 60-64 years, but exceeds 30% in those aged 90+ years [1]. The average life expectancy is increasing, but even more important from a dementia perspective, is that the proportion of the world's population aged over 80 years is increasing rapidly [2]. This translates into an expected doubling of people living with dementia every 20 years: from 35.6 million in 2010, to 65.7 million in 2030, and 115.4 million in 2050 [1]. Dementia is the leading contributor to disability and dependence among older people worldwide [1], and the personal and societal costs are huge [3].

Several recent population-based studies in Europe and North America have indicated that the age-specific incidence of dementia is declining [3-5]. The observed decline is modest and might not affect the expected dramatic increase in dementia prevalence to any major degree. It has been a matter of discussion whether the observed trend is due to better cardiovascular (CV) health status, higher educational level, or other life-style factors [6, 7]. In any case, it highlights the existence of modifiable risk factors for cognitive decline and dementia [8-10]. If these risk factors could be identified, and then properly modified, the benefit to society and the affected families would be substantial. Up to 25% of dementia cases may be prevented if dementia onset could be delayed by only 2 years [9, 11, 12], which is good news, since we currently lack effective treatments for dementia.

If the goal of dementia prevention is to be reached, a better understanding of the complex relationship between risk factors and cognition is necessary. In this thesis, observational associations between vascular factors, cognitive function, and dementia were investigated.

1.2 Cognitive decline and dementia

Cognition and age-related cognitive decline

Cognition can be defined in different ways, depending on the context in which the term is used. Therefore, it has different meanings for a linguistic researcher, a neuroscientist, and a computer scientist. According to the Oxford dictionary, cognition is defined as

> "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses" [13].

From a medical point of view, the criteria for neurocognitive disorders in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) [14] are based on six key domains of cognitive function: complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition. Identifying the domains affected in a patient can help establish the etiology and severity of the neurocognitive disorder.

All individuals are subject to age-related cognitive decline as part of the normal ageing process [15-17], although the inter-individual variation is large. The cognitive domains that primarily deteriorate with age are memory, executive function, and processing speed ('fluid' mental abilities), whereas 'crystallized' mental abilities, such as language skills, are more preserved [18]. Those abilities are called crystallized because they rely on knowledge and experience, in contrast to the fluid abilities, which require more flexibility. It should be noted that studies on cognitive function in normal ageing are prone to various kinds of bias. Cohort effects must be taken into consideration in cross-sectional studies, and selective survival and attrition are methodological problems in longitudinal studies.

Dementia

Dementia is a syndrome characterized by a decline in cognitive function severe enough to interfere with independence in everyday activities. In DSM-5, dementia has been replaced by major neurocognitive disorder, but the two terms are almost interchangeable [14]. The diagnostic criteria for major neurocognitive disorder are listed in Table 1. As can be seen, memory impairment is no longer a necessary requirement, as it was in DSM-IV [19]. Consequently, dementia disorders that do not primarily cause memory disturbances can now be properly diagnosed. According to DSM-5, the presumed etiological/pathological entity underlying the cognitive decline should be specified as Alzheimer's disease, frontotemporal lobar

degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/medication use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple etiologies, or unspecified. Further, it should be specified whether the cognitive decline is accompanied by a clinically significant behavioral disturbance, and if the current severity is considered to be mild, moderate, or severe.

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 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 neuropsychologic 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).

Over the years, several terms have been used to describe the intermediate stage between normal age-related cognitive decline and dementia. Examples include benign senescence forgetfulness [20], age-associated memory impairment (AAMI) [21], age-associated cognitive decline (AACD) [22], and cognitive impairment no dementia (CIND) [23]. Nowadays, the preferred term is mild cognitive impairment (MCI) [24], which is almost identical to minor neurocognitive disorder in DSM-5. In MCI, the cognitive impairments exceed those expected based on age and education, but are not severe enough to interfere with independence in everyday activities.

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia. Alone or in combination with other conditions, it accounts for the majority of dementia cases [3]. AD is a neurodegenerative disease, with amyloid plaques and neurofibrillary tangles as histologic hallmarks. In most cases, a specific pattern of brain atrophy, as well as a specific pattern of cognitive impairment can be seen, with episodic memory being affected first [3]. The clinical course is slowly progressive, and encompasses the whole range from preclinical AD [25] to dementia due to AD (from now on referred to as AD dementia). The diagnostic criteria for major neurocognitive disorder due to AD according to DSM-5 are listed in Table 2.

Table 2.
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 at least two cognitive domains.
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.
	b. Steadily progressive, gradual decline in cognition, without extended plateaus.
	c. No evidence of mixed etiology.
D.	The disturbance is not better explained by cerebrovascular diseases, another neurodegenerative disease, the effects of a substance, or another mental, neurologic, or systemic disorder.

Vascular cognitive impairment

The term vascular cognitive impairment (VCI) has been coined to encompass all forms of cognitive impairment caused by cerebrovascular disease and pathology [26]. It thus includes the whole spectrum from subtle cognitive deficits to vascular dementia (VaD). The etiology of VCI is heterogeneous, and the clinical presentation is variable [27]. Often, executive function and psychomotor speed are the cognitive domains primarily affected [26, 28, 29]. Non-cognitive symptoms, such as depression, apathy, and urinary incontinence, are frequent and prominent [27]. Based on the clinical presentation and the neuroimaging findings, VaD can be broadly divided into cortical and subcortical VaD [27, 30]. Cortical VaD is mainly caused by large-vessel disease and subcortical VaD mainly by small-vessel disease.

Just as for AD dementia, and for dementia in general, there are many different diagnostic criteria for VaD [27, 31]. These criteria differ in fundamental ways, and are not interchangeable [32]. For example, the *National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS-AIREN) criteria require focal neurologic signs to be present for a diagnosis of VaD [33]. This is also a requirement in the *International Classification of Diseases*, 10th edition (ICD-10) [34] but not in the DSM-IV [19] or DSM-5 [14]. Therefore, the prevalence of VaD in a population differs depending on the diagnostic criteria used [35]. Most authors agree that vascular factors, alone or in combination with other pathologies, are the second leading cause of dementia worldwide [36]. The diagnostic criteria for major vascular neurocognitive disorder according to DSM-5 are given in Table 3.

Table 3.
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.

Mixed dementia

A diagnosis of mixed dementia, or major neurocognitive disorder due to multiple etiologies, as it is called in DSM-5, is used when

> "there is evidence from the history, physical examination, or laboratory findings that the neurocognitive disorder is the pathophysiological consequence of more than one etiological process, excluding substances" [14].

In clinical practice, mixed dementia often means that both Alzheimer and cerebrovascular pathology are judged to significantly contribute to the disorder. However, other conditions could of course also contribute, and it is therefore recommended to always specify the contributing conditions [36]. Given that the ageing brain is exposed to many different age-related and pathologic processes simultaneously, mixed dementia is common in the older ages [37].

AD or VaD?

In the 19th century, several physicians described an association between postmortem cerebrovascular changes and cognitive impairment preceding death [38]. Up until the 1960s, the prevailing view was that 'senile dementia' was caused mainly by vascular factors, and the term 'arteriosclerotic dementia' was in common use [27, 38, 39]. Although Alois Alzheimer described the condition that later became known as AD already in 1907 [40], it was considered quite rare, and mainly associated with early-onset or 'presenile' dementia. This view was challenged by seminal studies in the 1960s, which established AD as the leading cause of dementia [41, 42]. Cerebrovascular disease was thought to cause dementia only when large cortical infarcts were present, and the term 'multi-infarct dementia' was coined in the 1970s [43].

During the last 20 to 30 years, this view has once again been challenged. It is now recognized that large cortical infarcts are just one of the causes of VaD. Indeed, subcortical VaD is probably the most common subtype [27]. Also, the dichotomous division between AD dementia and VaD has been questioned, and they are

nowadays often considered two ends of a continuum rather than two distinct entities [44]. Population-based studies have found that a majority of people over 80 years of age have radiologic and pathologic evidence of cerebrovascular disease [45, 46]. This is true also for patients with a clinical diagnosis of dementia [47, 48], and to elucidate if and when these changes contribute to the clinical symptoms is difficult. In other words: which of the cerebrovascular changes are clinically relevant? Markers of cerebrovascular disease, such as white matter hyperintensities (WMH) and lacunar infarcts, have been associated with cognitive decline and dementia at the population level [49], but these findings cannot automatically be extrapolated down to the individual patient level [50].

If there is evidence of both Alzheimer and cerebrovascular pathology in the brain of a patient with dementia, the combination of these pathologies can be interpreted in different ways:

a) Only one of the pathologies contributes to the clinical symptoms.

b) Both pathologies contribute to the clinical symptoms, i.e., mixed dementia.

c) One of the pathologies does not contribute to the clinical symptoms but increases the clinical expression of the other pathology. For example, the presence of small brain infarcts can increase the clinical expression of AD [51, 52].

To complicate the diagnostic procedure even further, vascular risk factors have been shown to increase the risk not only of VaD but also of AD dementia [48, 49, 53-55]. Whether the increased risk of AD dementia is caused by increased levels of AD pathology in the brain, or whether it is just a reflection of cerebrovascular pathology lowering the threshold for clinical AD symptoms, remains a matter of debate [56]. Interestingly, some studies have found an association between higher blood pressure (BP) and AD biomarkers in the cerebrospinal fluid and in the brain [57, 58], but these results do not prove causality. The fact that the associations of vascular factors with cognitive decline and dementia are complex and not fully understood was an important theoretical background and a motivation for undertaking the studies of this thesis.

1.3 Biomarkers and risk factors

A biomarker can be defined as

> "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" [59].

This definition encompasses a broad range of biological markers, and they can be subdivided into genetic, circulating, and tissue biomarkers [60]. Plasma copeptin is an example of a circulating biomarker, and carotid-femoral pulse wave velocity (c-f PWV) is a tissue biomarker.

Terms like risk factor, risk marker, risk indicator, and determinant are often used more or less interchangeably as factors that are statistically related to the outcome of interest [61]. A narrower definition of a risk factor is

> "an environmental, behavioral, or biologic factor confirmed by temporal sequence, usually in longitudinal studies, which, if present, directly increases the probability of disease occurring, and if absent or removed reduces the probability" [62].

Thus, using this definition, a risk factor should be part of the causal chain leading to the outcome of interest. A risk marker, on the other hand, is merely a characteristic that is statistically associated with the outcome and does not have to be part of the causal chain leading to it [62]. Since causality is difficult to prove [63], most novel biomarkers emerging in the field of cognitive epidemiology should preferably be labeled risk markers, not risk factors.

Risk factors for cardiovascular disease

Cardiovascular disease (CVD) is a class of chronic diseases involving the heart and/or the arteries, with atherosclerosis most often being a key component in the pathogenesis [64]. The most common clinical manifestations of CVD are coronary heart disease, cerebrovascular disease, and peripheral artery disease (PAD) [65]. These overt CVDs are typically preceded by a long period of subclinical CVD [60]. Measures of subclinical CVD include left ventricular hypertrophy, microalbuminuria, increased carotid-intima media thickness (cIMT), decreased ankle-brachial index (ABI), as well as the measures of arterial stiffness discussed in this thesis.

Non-modifiable risk factors for CVD include age, sex, and family history, and the major modifiable risk factors include hypercholesterolemia, diabetes, hypertension,

obesity, smoking, and physical inactivity [66]. Given that these have been recognized since the 1960s [67], they are often labeled 'traditional' or 'established', in contrast to 'novel' or 'emerging'. During recent years, there has been an increasing interest in finding novel risk factors/markers for CVD [68-70]. This interest has been fueled by the fact that a large proportion of patients experiencing their first CVD event have only one or none of the traditional CV risk factors [60, 71] and are stratified as being at low CV risk [68].

Finding novel risk factors/markers could serve both to increase the knowledge of disease mechanisms and causes, and to improve risk prediction in the individual patient [72]. In this thesis, the main focus was on elucidating disease mechanisms and causes, and hence, statistical measures of association (based on regression models) were used. If the focus had been on risk prediction in the clinical setting, tests of discrimination and reclassification would have been necessary, as well as a discussion about practical issues and cost-effectiveness [60, 73].

1.4 Risk factors for cognitive decline and dementia

As pointed out earlier, all individuals are subject to age-related cognitive decline as part of the normal ageing process [15, 17]. Dementia is probably in most cases qualitatively different from this process, and does not just represent the upper end of a continuum [16, 74]. Therefore, risk factors for cognitive decline in the elderly might not be identical to risk factors for dementia, even though a large overlap certainly exists [17]. This distinction is seldom made in observational cognitive epidemiology, and cognitive decline over time is often used as a surrogate marker for dementia. In this context, it can be stressed that age-related cognitive decline may by itself significantly affect the well-being of the individual [17].

Since AD dementia is the most common subtype of dementia, and since mixed dementia is common, it is often difficult to separate risk factors for AD from risk factors for all-cause dementia. The finding that vascular risk factors are risk factors not only for VaD but also for AD dementia [49, 53-55] adds to the complexity. In the brief overview provided below, the risk factors pertain mainly to all-cause dementia, but in some cases mainly to AD dementia.

Dementia is a multifactorial disorder, and there rarely exists one single sufficient cause. Therefore, the interplay between risk factors is more important than the risk factors themselves. In this context, a life-course approach to the etiology of dementia is preferable [75, 76]. The life-course approach aims to identify periods during life when the risk factors exert their main effects. Further, it examines how factors early in life (even prenatally) are associated with health and disease later in

life. This is relevant when interpreting studies of the association between risk factors and cognition. For example, intelligence test scores in childhood have been associated with the presence of CV risk factors in midlife [17, 77], which affects the interpretation of studies on the association between midlife CV risk factors and late-life cognitive function.

Another important aspect of the association between risk factors and dementia is the concept of cognitive reserve [78, 79], meaning that compensatory mechanisms can enable the individual to tolerate brain pathology without having overt cognitive symptoms. The cognitive reserve is not static but can be modulated by, for example, educational attainment.

The fact that a modifiable risk factor is associated with risk of dementia in an observational study does not provide evidence of clinical benefit of eliminating the risk factor. It has generally been difficult to translate promising observational evidence into evidence supporting prevention of cognitive decline and dementia [80, 81]. For example, of all the randomized controlled trials investigating the effect of BP lowering on dementia risk in the general population, only one found a statistically significant effect [82, 83]. Further, several large-scale multidomain intervention trials have been launched in recent years, but the results thus far have not been convincing [84-86], even though some beneficial effects have been noted.

Age

Older age is the strongest risk factor for cognitive decline and dementia [3]. Dementia before 65 years of age is rare, but the risk roughly doubles every 5 years thereafter [27].

Genetic factors

Pathogenic mutations with autosomal dominant inheritance in several different genes cause rare forms of early-onset familial AD [3]. In addition, susceptibility loci, such as the ε4 allele of the *APOE* gene, are associated with an increased risk of sporadic AD, and the heritability of AD is estimated to be substantial [87]. The genetic contribution to VaD has not been studied in such detail, but one example is mutations in the *NOTCH3* gene, causing the rare familial syndrome CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), where cognitive impairment at a relatively young age is a core feature [88].

Vascular, metabolic, and nutritional factors

The brain is highly vascularized and has a low resistance to flow, which renders it susceptible to CV dynamics. The brain consumes up to 20% of the body's oxygen and other nutrients, all of which are supplied to it by the arteries [89]. Accordingly, a well-functioning vascular system is essential for the brain.

Hypertension is associated with an increased risk of stroke in a continuous manner [90]. Because stroke increases the risk of dementia [50, 91], a strong and straightforward association between hypertension and dementia could be assumed. However, the association of BP [92-95], as well as cholesterol and obesity [49, 89, 96, 97], with risk of dementia and cognitive decline has been found to be complex. When measured in midlife, increased levels of these traditional CV risk factors have been reported to convey an increased risk not only of VaD but also of AD dementia, as well as of cognitive decline [49, 83, 98-101]. When measured in late-life, the reported associations between CV risk factors and dementia have often been neutral or inverse, with lower levels conveying an increased risk [3, 44, 102]. The effect modification by age is reflected in the differences between the CAIDE risk score [99] and the Late-life Dementia Risk Index [103]. For example, in the CAIDE risk score, a high body mass index (BMI) in midlife confers an increased risk of future dementia, while in the Late-life Dementia Risk Index, a low BMI confers an increased risk. Given the effect modification by age, and because the patients who seek healthcare with cognitive complaints are predominantly elderly, we obviously need new markers of the relationship between vascular factors and dementia. To add further complexity, elderly people with low levels of the traditional CV risk factors might in fact constitute a mixture of two subgroups: those with low levels as a result of multiple chronic diseases and frailty, and those with low levels due to generally good health.

Markers of subclinical CVD, often regarded as 'novel' vascular risk markers, have been associated with cognitive function as well as with dementia risk, even though the reported results have sometimes been conflicting. Markers of subclinical CVD include markers of atherosclerosis, such as coronary artery calcification (CAC) [104], cIMT [105-107], and ABI [108]. They also include markers of arterial stiffness, which was the main focus in this thesis.

Having a clinically manifest CVD increases the risk of future cognitive decline and dementia. It could be debated how much of this risk increase is mediated by causal mechanisms, and how much is mediated by shared risk factors and common pathophysiology. Heart failure [109, 110], atrial fibrillation [111], and coronary artery disease [49] have repeatedly been shown to increase the risk of dementia. A previous stroke increases the risk by a factor of 2 to 5 [50], and the presence of

subclinical vascular brain injury, such as silent brain infarcts and WMH [50, 112-114], also predicts cognitive decline and dementia.

Diabetes mellitus and glucose metabolism disturbances are well-recognized risk factors for cognitive decline and dementia, including both VaD and AD dementia [9, 115, 116]. Recent research has indicated that the increased risk of AD dementia in those with diabetes is not mediated by increased AD pathology in the brain, but by increased cerebrovascular pathology [117, 118]. This is in line with findings from the seminal Nun Study, where the presence of small brain infarcts increased the clinical expression of AD manifold [51].

Even though the associations reported between CV risk factors and diseases on the one hand, and cognitive decline and dementia on the other hand, are usually quite weak (small effect sizes), it is important to acknowledge that these factors can still be important from a public health perspective. Since CV risk factors and diseases are so common, quite a substantial proportion of the dementia prevalence might be attributable to them [11, 119]. Hence, given that the associations are causal, prevention of cognitive decline and dementia might be substantial at the population level if the risk factors are modifiable.

Nutritional factors, e.g., intake of fish and omega-3 polyunsaturated fatty acids, Mediterranean diet, antioxidants, and certain vitamins, have been associated with dementia risk in some, but not all, studies [9, 120, 121].

Psychosocial and lifestyle factors

High educational achievement in early life reduces the risk of late-life dementia [3, 9, 122]. This association might be causal, mediated by an increased cognitive reserve, but educational achievement might also be a surrogate marker of, for example, high socioeconomic status and better early life conditions and living environment. Social engagement, occupational achievement, low levels of midlife psychological stress, participation in mentally stimulating activities, and regular physical activity have all been associated with a decreased dementia risk [8, 9, 122-124].

Other factors

The list of factors that have been associated with an increased risk of cognitive decline and dementia is long and diverse. Some examples of such factors include traumatic brain injury [125], use of benzodiazepines [120], depression [120], chronic kidney disease [126], and physical frailty (‘motoric cognitive risk syndrome’ [127]) [128, 129].

1.5 Arterial stiffness

The idea that stiff arteries reflect biological, as opposed to chronological, age is not new. Already in the 17th century Thomas Sydenham (1624-1689) wrote that "*a man is as old as his arteries*" [130]. During the latter half of the 19th century Fredrik Akbar Mahomed (1849-1884) and others invented sphygmographs that could convey the pressure waveform from the radial artery to smoked paper moving at constant speed. The technique was used by contemporary life insurance companies to decline applicants with 'anticipated arterial senility' [131]. The interest in arterial stiffness and pulse wave analysis declined rapidly after the cuff sphygmomanometer for measurement of brachial BP was introduced in the early 20th century, and has only recently become a major focus of clinical research again [131].

The aorta and its proximal branches have two primary functions: to deliver blood at a steady pace to the body's organs (conduit function), and to dampen the pulsations caused by the contracting heart (cushioning function). This is achieved by the pronounced elasticity of the large arteries. With age, the amount of elastic material in the arterial wall decreases and the relative amount of collagen increases, leading to a progressive stiffening known as arteriosclerosis [132]. Arteriosclerosis should not be confused with atherosclerosis, which consists of focal accumulation of lipids, calcium, and inflammatory cells in the innermost layer of the arteries [133]. However, arteriosclerosis and atherosclerosis often coexist, and they share several risk factors. The arterial stiffening process is accelerated by a number of conditions, including hypertension, diabetes, and end-stage renal disease. The concept of early vascular ageing (EVA) has been developed to describe individuals with advanced arteriosclerosis early in life [134-136].

Measures of arterial stiffness have been suggested to reflect the cumulative damage of known and unknown risk factors on the arterial wall over a long period of time, and thus to be good indicators of general CV health status [134, 137]. In contrast, measures of the traditional CV risk factors fluctuate considerably over time and can only be seen as snapshots. Furthermore, measures of arterial stiffness might identify patients in whom CV risk factors have translated into real risk, i.e., reflecting the individual's susceptibility to the risk factors. In this context, arterial stiffness can be conceptualized as a 'target organ damage' (TOD) [135, 138]. Stiffening of the large central arteries leads to 'upstream' and 'downstream' pathologic consequences. Upstream, the heart is exposed to increased strain caused by the increased left ventricular load, leading to ventricular hypertrophy, ischemia, and heart failure [131]. Downstream, flow pulsations are transmitted into vulnerable organs such as the brain and the kidneys, where the pulsatile energy is dissipated and damages small fragile vessels [139].

Measures of arterial stiffness

There are many different indices of arterial stiffness, and they partly reflect different aspects of hemodynamic ageing. The pulse wave generated by the contracting heart travels faster in stiff arteries, and the pulse wave velocity can be measured non-invasively. The gold standard is to measure the pulse wave velocity from the carotid to the femoral artery (c-f PWV), i.e., a measure of the aortic stiffness [137, 140]. Pulse wave velocity can also be measured between other arterial sites, for example the brachial and the tibial artery (brachial-ankle pulse wave velocity, b-a PWV). However, peripheral (muscular) arteries do not undergo the same stiffening process with age as the central arteries, and therefore c-f PWV and b-a PWV are not interchangeable [137].

Age is the strongest predictor of c-f PWV, followed by BP [141, 142]. In line with the notion that arterial stiffness in some respects is a reflection of biological ageing, c-f PWV has been associated with physical function and frailty in the elderly [143, 144]. In the Malmö Diet and Cancer study, c-f PWV was associated with hemodynamic (BP and heart rate) as well as with non-hemodynamic factors (waist circumference, fasting glucose level, insulin resistance, and dyslipidemia: high triglycerides, low HDL cholesterol) [145]. C-f PWV has been shown to contribute added value beyond traditional CV risk factors in predicting CV events and death [146-148]. Further, several studies have reported that patients at intermediate CV risk can be reclassified into lower or higher risk categories based on c-f PWV [146, 149]. Reference values for c-f PWV in the general European population were published in 2010 [142].

As a direct result of the arterial stiffening process, systolic BP increases and diastolic BP decreases [141]. This explains why systolic BP increases throughout life, while diastolic BP peaks at age 50-60 years, and then decreases [150]. Thus, the pulse pressure (PP = systolic BP – diastolic BP) can be considered a marker of arterial stiffness. However, PP is also affected by other factors, e.g., the heart rate, the peripheral vascular resistance, and the heart's stroke volume [141].

Owing to the elasticity of the aorta and its proximal branches, central (aortic) systolic BP is lower than brachial systolic BP in young, healthy people [151]. As the large central arteries stiffen, this difference levels off, and central BP therefore reflects arterial stiffness [141, 152]. Other factors, such as the magnitude of the pressure waves reflected from the periphery back to the heart, also affect the level of central BP [153]. This explains why c-f PWV and central PP are only modestly correlated (Pearson correlation, $r = 0.38$, in the study population of Paper I). Given that the heart, the brain, and other vital organs are exposed to aortic rather than brachial BP, it has been suggested that central BP is a better predictor of CV events than brachial BP. Some recent studies [147, 152, 153], but not all [149], have found

support for this hypothesis. Furthermore, in a recent systematic review and meta-analysis [154], central compared with brachial BP seemed to be more strongly associated with different indices of preclinical TOD. Since different anti-hypertensive medications have different effects on central and brachial BP [155, 156], it is important from a clinical point of view to determine if central BP is superior to brachial BP in risk prediction. For example, beta blockers reduce central BP to a lesser degree than other anti-hypertensive drugs, despite similar effects on brachial BP [155]. Central BP can be measured invasively during surgery. It can also be estimated non-invasively, most commonly by estimating the aortic pressure waveform from the radial artery pressure waveform [157, 158] as done in this thesis.

There are other measures that, at least partly, reflect arterial stiffness. The augmentation index quantifies how much the reflected pressure waves augment the central PP [159]. Arterial stiffness can also be measured locally, for example in the carotid artery, with an ultrasound technique called echo-tracking [137].

Association of c-f PWV with brain structure and function

Independently of traditional CV risk factors, c-f PWV has been reported to predict the risk of clinically manifest stroke [146, 160, 161]. Also, c-f PWV has repeatedly been associated with markers of cerebral small-vessel disease [162], including WMH [163-165] and lacunar infarcts [166]. Further, higher c-f PWV has been associated with lower total cerebral brain volume [165], as well as with medial temporal lobe atrophy [167]. In preliminary studies, measures of arterial stiffness have been associated with beta-amyloid deposition in the brain [58, 168], but these studies need replication before firmer conclusions can be drawn.

Several systematic reviews have summarized studies reporting on the association between c-f PWV and cognitive test results [162, 169-172]. Generally, after adjustment for demographics and traditional CV risk factors, higher c-f PWV has been associated with worse results on cognitive tests. This applies both to population-based [163, 173-181] and patient-based [182-187] studies, and cross-sectionally [163, 173-176, 179, 181, 183, 184] as well as longitudinally, measuring cognitive decline over time [177-180, 182, 185-187]. However, not all studies have found significant associations [165, 188-190], and mixed results regarding which cognitive domains that primarily are affected have been reported. As noted in recent reviews [171, 172], the somewhat heterogeneous results across studies can to some extent be explained by differences in study populations, cognitive tests used, and statistical analyses, including adjustment for different covariates. The results also appear more comprehensible when the generally small effect sizes are considered.

The fully adjusted results from the key population-based studies are summarized below:

- In the Rotterdam Study [176], a cross-sectional association was found between c-f PWV and the Stroop test, which is primarily a test of executive function. No cross-sectional associations with three other cognitive tests, and no longitudinal associations with cognitive decline over time, were found.
- Two separate publications from the AGES-Reykjavik Study [163, 173] reported that higher c-f PWV was cross-sectionally related to lower memory scores, but not to processing speed or executive function.
- In the Framingham Offspring Study, no independent cross-sectional associations were found between c-f PWV and tests of memory or executive function after full adjustment [165]. Longitudinally, baseline c-f PWV was associated with greater decline in executive function over 6.4 years of follow-up [177]. In the Framingham Third Generation Cohort Study [175], examining young and middle-aged adults, an adjusted cross-sectional association was seen in 1 out of 9 cognitive tests (Trail B-A, measuring processing speed and executive function).
- In the Health ABC Study, inverse associations were found both cross-sectionally and longitudinally between c-f PWV and measures of global cognitive function, psychomotor speed, and perceptual speed [179, 180].

The association between c-f PWV and dementia has not been studied in such detail. In a patient-based, cross-sectional study, demented patients had higher c-f PWV compared with healthy controls, and c-f PWV was higher in patients with VaD than in patients with AD dementia [183]. These findings could not be replicated in a small British study [191]. In a recent publication from the ARIC-NCS study, no independent cross-sectional association was found between c-f PWV and prevalent dementia [192]. Except for Paper IV in this thesis, two large population-based studies have reported on the prospective association between c-f PWV and incident dementia. Over 4.4 years of follow-up in the Rotterdam study, c-f PWV did not predict all-cause dementia (156 dementia cases, adjusted HR 0.91, 95% CI 0.75-1.10 per 1 SD increase in c-f PWV), or any subtype of dementia, although a trend was noted for VaD [176]. Over 10 years of follow-up in the Framingham Offspring study, c-f PWV did predict all-cause dementia adjusted for age, sex, education, and *APOE* ε4 allele status (77 dementia cases, HR 1.35, 95% CI 1.05-1.74), but the association disappeared after full adjustment including mean arterial pressure (MAP) (HR 1.17, 95% CI 0.85-1.61) [193]. When the authors conducted secondary subgroup-analyses, c-f PWV predicted dementia in nondiabetic individuals, but such analyses are quite speculative.

Association of central BP with brain structure and function

Several publications have reported on the association between central BP and cognitive performance. In the AGES-Reykjavik Study as well as in the Framingham Offspring Study, central PP was cross-sectionally associated with lower memory scores [163, 165]. In the Maastricht Study, no association was found between central BP and the cognitive domains tested [188]. Longitudinally, central PP has been associated with a decline in abstract reasoning [177]. An association between central PP and lower total cerebral brain volume was found in the Framingham Offspring Study but not in the AGES-Reykjavik Study [163, 165]. None of these studies found associations with WMHs or silent cerebral infarcts.

Of note, the above mentioned studies did not report whether central BP was more closely associated with the cognitive outcome than brachial BP was. Given the very high correlation between central and brachial BP [194], the results can consequently not judge whether central BP is better than brachial BP in this regard. Pase *et al.* conducted a cross-sectional study of 493 healthy volunteers aged 20-82 years in Melbourne, Australia [195]. They found that higher central systolic BP and PP were associated with poorer Stroop processing, poorer recognition memory, and poorer processing speed, whereas brachial BP was only associated with poorer Stroop processing. Regarding dementia, no associations were found between central PP and all-cause dementia or AD in the Framingham Offspring Study [193], and central PP did not show stronger effect sizes (hazard ratios) compared with brachial PP.

1.6 Vasopressin and copeptin

Vasopressin, also known as antidiuretic hormone, is a neurohypophyseal hormone involved in osmoregulation, stress response, glucose metabolism, and control of vascular tone [196]. Vasopressin also acts locally as a neuropeptide in the brain, where it has been suggested to affect learning and memory [197], and seems to be involved in behavior and social interaction [198]. Due to its mean half-life of only 24 minutes and other pre-analytical factors, vasopressin is cumbersome to measure in plasma [199]. Copeptin, the stable C-terminal part of the vasopressin precursor peptide, is secreted in equimolar amounts to vasopressin, and is considered to be a reliable surrogate marker for vasopressin [199]. Therefore, copeptin is not so interesting *per se*, but is interesting because it reflects the levels of vasopressin.

Recent studies have found that plasma copeptin is an important risk marker for CV and metabolic disease risk [200]. In population-based studies, an elevated level of copeptin has been associated with an increased incidence of diabetes mellitus [201, 202], and with diabetes-related CVD [203, 204]. Further, it has been associated with

the metabolic syndrome [205, 206], and with total and CV mortality [207]. In patient-based studies, an elevated level has been associated with a worse prognosis in many diseases, including heart failure [208] and stroke [209]. Copeptin has been used to rule out myocardial infarction in the acute setting [210]. Whether vasopressin is causally related to the development of cardiometabolic disease, or just a marker of increased disease risk, is an area of present research [200]. If causality can be proven, it might be beneficial for individuals with high plasma copeptin to drink more water, since increased water intake decreases vasopressin levels [211].

Only one study has investigated the association between copeptin and cognitive function: Tufvesson *et al.* reported that elevated baseline plasma copeptin predicted worse results on A Quick Test of cognitive speed (AQT) after 16 years of follow-up [212]. No previous study has reported on the association between copeptin and risk of dementia.

2 Aims

The overall aim of the research presented in this thesis was to gain further knowledge of the complex association between vascular factors and cognitive function.

The specific aims were:

- To assess the cross-sectional association between c-f PWV, a marker of arterial stiffness, and cognitive test results (**Paper I**).
- To assess the association of brachial as well as central (aortic) BP with cognitive function, both cross-sectionally and with brachial BP measured 17 years before cognitive testing (**Paper II**).
- To investigate if the baseline level of plasma copeptin, a marker of vasopressin, predicts incident dementia and dementia subtypes over 4.2 years of follow-up (**Paper III**).
- To assess the cross-sectional association between c-f PWV and prevalent dementia. Further, to investigate if baseline c-f PWV predicts incident dementia and dementia subtypes over 4.6 years of follow-up (**Paper IV**).

3 Material and methods

3.1 Study populations

The Malmö Preventive Project (MPP) is a large-scale population-based cohort study in the city of Malmö, located in southern Sweden. Baseline examinations were conducted from 1974 to 1992, with the initial aims of screening for CV risk factors and alcohol abuse in the general population [213]. A total of 33 346 individuals were screened (age range 27-61 years, mean age 45.7 years, participation rate 71%). A reexamination of 18 240 surviving participants still living in the Malmö area was conducted from 2002 to 2006 (age range 56-85 years, mean age 68.7 years, participation rate 72% of surviving baseline participants) [214]. The reexamination included a self-administered questionnaire, clinical measurements, and blood sampling. A flow chart is presented in Figure 1.

When the baseline examinations of MPP were almost completed, a new large-scale population-based cohort study was launched in Malmö: the Malmö Diet and Cancer study (MDC) [215]. For the baseline examinations 1991-1996, all men born 1923-1945 and all women born 1923-1950 living in the city of Malmö were invited to participate. Women born 1946-1950 were included to make it possible to study premenopausal breast cancer. The only exclusion criteria were inadequate Swedish language skills and mental disability. With the initial aim of exploring the relationship between diet and cancer, 28 449 individuals were screened (age range 44-73 years, mean age 58.1 years, participation rate 41%). At the time of MDC inclusion, a random sample from the cohort was invited to a sub-study focusing on carotid artery morphology and CV risk factors, and 6103 individuals participated in this 'Cardiovascular arm' of MDC (MDC-CV) [216]. About 13% of the MDC-CV participants were born outside Sweden, mainly in Denmark, Yugoslavia, Germany, Poland, Finland and Hungary. A total of 3734 MDC-CV participants were reexamined between 2007 and 2012 (age range 61-85 years, mean age 72.5 years, participation rate 76% of surviving baseline participants) [145, 217] – see Figure 1. The reexamination included a self-administered questionnaire, clinical measurements including c-f PWV and central BP, cognitive testing, and blood sampling. The characteristics of the participants in the MPP reexamination and the MDC-CV reexamination are shown in Table 4.

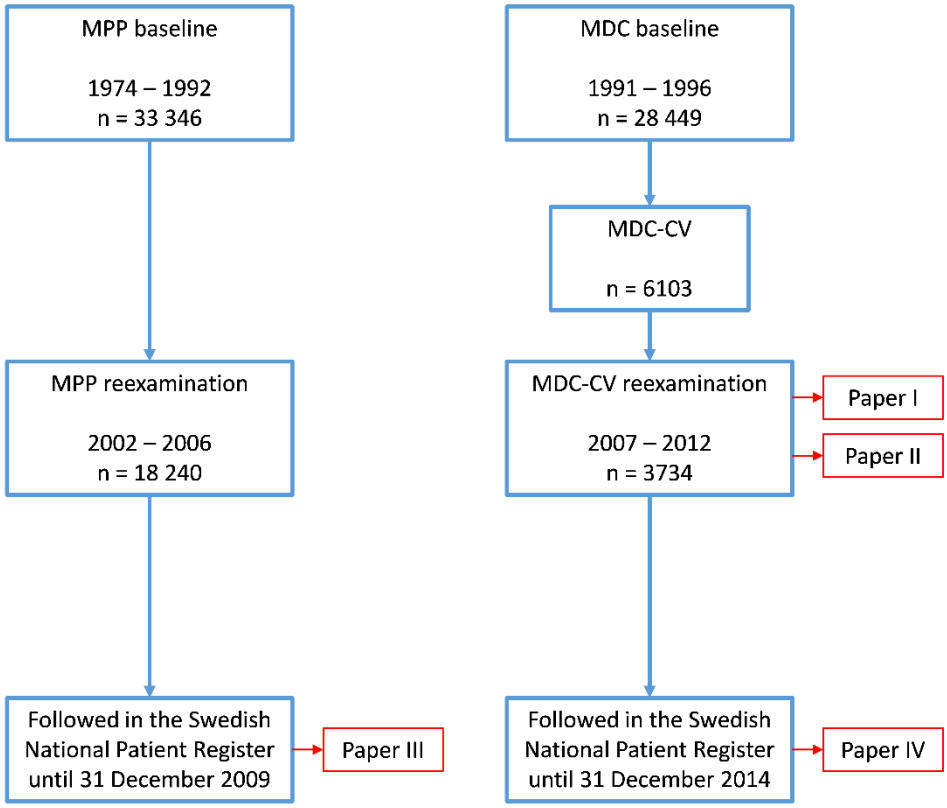

Figure 1.
Flow charts of the Malmö Preventive Project (MPP) and the Cardiovascular Arm of the Malmö Diet and Cancer study (MDC-CV). Description of the study populations.

Table 4.
Characteristics of the participants in the MPP reexamination 2002-2006 (n = 18 240) and the MDC-CV reexamination 2007-2012 (n = 3734).

	MPP reexamination	MDC-CV reexamination
Age, years	68.7 ± 5.8	72.5 ± 5.6
Men, n (%)	11 558 (63.4)	1522 (40.8)
Education ≤ 8 years, n (%)	10 113 (57.4)	1501 (41.5)
Copeptin, pmol/l (n = 5410)	7.2 (4.3-12.0)	
c-f PWV, m/s (n = 3056)		10.5 ± 2.5
AQT, s (n = 3310)		74.1 ± 20.4
MMSE, points (n = 3329)		28.1 ± 1.9
Brachial BP, mmHg		
Systolic BP	144.8 ± 20.1	131.0 ± 17.1
Diastolic BP	83.5 ± 10.7	73.4 ± 8.8
PP	61.3 ± 14.1	57.5 ± 12.9
Central BP, mmHg (n = 3001)		
Systolic BP		122.3 ± 16.8
Diastolic BP		74.4 ± 9.0
PP		48.0 ± 12.3
PP amplification, ratio		1.21 ± 0.11
BMI, kg/m^2	27.2 ± 4.2	26.7 ± 4.3
LDL cholesterol, mmol/l	3.6 ± 1.0	3.3 ± 0.9
Diabetes mellitus, n (%)	1942 (10.6)	578 (15.6)
Current smoking, n (%)	3114 (17.1)	357 (9.9)
History of stroke, n (%)	666 (3.7)	108 (2.9)
BP-lowering drugs, n (%)	6968 (38.2)	1882 (50.4)

Continuous variables are presented as mean ± SD or median (interquartile range). Categorical variables are presented as number (%).

Paper I

When Paper I was drafted, previous studies on the association between c-f PWV and cognitive test results had reported conflicting findings. Therefore, we analyzed this association cross-sectionally in the MDC-CV reexamination. Since the validity of cognitive tests administered in languages other than a person's native language can be questioned, participants born outside Sweden (n = 472) were excluded. After further exclusion of participants with missing data on either cognitive tests (n = 405)

or c-f PWV (n = 678), the study population comprised 2637 individuals (mean age 72.1 years; 60.8% women).

Paper II

Observational studies of the association between brachial BP and cognitive function have reported heterogeneous results. Central BP might be more strongly related to cognitive function than brachial BP, but only one previous study has reported on this issue [195]. Therefore, using data from the MDC-CV cohort, we assessed the cross-sectional association of brachial and central BP with cognitive test results at the MDC-CV reexamination. Further, we assessed the association of brachial BP measured at the MDV-CV baseline examination and cognitive test results at the reexamination. Stroke affects the association between BP and cognition [83], and therefore individuals with a history of stroke were excluded (n = 108). In addition, the same exclusion criteria as used in Paper I were applied (missing data on central BP, n = 733), leaving a study population of 2548 individuals (mean age 55.4 years at the MDC-CV baseline examination, and 72.1 years at the MDC-CV reexamination; 61.4% women).

Paper III

An elevated level of plasma copeptin has been associated with CV and metabolic disease risk. The association between copeptin and risk of dementia has not previously been reported. Therefore, we investigated whether plasma copeptin could predict incident dementia and dementia subtypes. The study population was derived from the 18 240 individuals in the MPP reexamination, and the timing of this reexamination was considered the baseline time point. Copeptin was retrospectively measured in frozen plasma from all participants who developed dementia up until 31 December 2009, as well as in a random sample of 5100 individuals in the cohort. Thus, a case-cohort study design was used. Following exclusion of 54 cases with prevalent dementia at the MPP reexamination, the study population comprised 5356 individuals (mean age 69.3 years at the MPP reexamination; 30.2% women).

Paper IV

C-f PWV has been associated with cognitive test results, as well as with markers of cerebral small-vessel disease. On the basis of these findings, some recent reviews have presumed that c-f PWV is also associated with an increased risk of dementia

[169, 170]. However, to date there is not enough evidence to support such a conclusion. Therefore, we assessed the association between c-f PWV measured at the MDC-CV reexamination and prevalent, as well as incident, dementia and dementia subtypes during register-based follow-up until 31 December 2014. Participants not born in Sweden were retained in the study population of Paper IV, because a diagnosis of dementia is not affected by Swedish language skills in the same way as results on cognitive tests are (Papers I and II). Thus, the only exclusion criterion was missing data on c-f PWV, leaving a study population of 3056 individuals (mean age 72.1 years at the MDC-CV reexamination, which was considered the baseline time point; 60.5% women).

3.2 Brachial blood pressure

At the MPP reexamination, brachial BP was measured twice with a mercury-column sphygmomanometer after five minutes of supine rest, and the mean values were calculated. At the MDC-CV baseline examination, brachial BP was measured once with a mercury-column sphygmomanometer after five minutes of supine rest. At the MDC-CV reexamination, brachial BP was measured with an OMRON M5-I IntelliSense® on three different occasions. First, it was measured once on the first day of visit after ten minutes of supine rest. Then, on the second day of visit, it was measured twice after five minutes of supine rest immediately before the assessment of c-f PWV. Finally, it was measured once in conjunction with the assessment of central BP.

MAP was calculated as diastolic BP + 1/3 × PP. In Papers I and IV, brachial BP measured immediately before the assessment of c-f PWV was used to calculate MAP. In Paper II, brachial BP measured in conjunction with the assessment of central BP was used; these BP values were measured right after c-f PWV had been assessed. Due to the c-f PWV measurement procedure, the participants had been resting in supine position in a quiet room for approximately 30 minutes when the BP measurements took place. Probably, this explains why the BP values were so low (Table 4). The brachial BP values measured on the first day of visit to the MDC-CV reexamination were markedly higher (mean systolic BP 143.4 mmHg, mean diastolic BP 83.0 mmHg).

3.3 Novel vascular risk markers

c-f PWV (Paper I, IV)

At the MDC-CV reexamination, c-f PWV was measured noninvasively using applanation tonometry (SphygmoCor®, AtCor Medical, Sydney, Australia – see Figure 2). With participants in supine position, rested for 5 minutes in a quiet room, ECG-gated carotid and femoral artery waveforms were sequentially obtained with a pressure sensitive probe. The carotid-femoral transit time was measured between the feet of the two waveforms. The distance between the recording sites was estimated as the distance between the femoral artery recording site and the suprasternal notch minus the distance between the carotid artery recording site and the suprasternal notch. C-f PWV (m/s) was calculated as c-f PWV = distance (meters) / transit time (seconds). In most cases (86.7%), three measurements per individual were obtained, and the results are based on the mean values of c-f PWV. The mean coefficient of variation between the c-f PWV measurements in the same individual was 6.3% (±SD 4.4%). The inter-observer variability between two technicians was tested twice. At one occasion, c-f PWV was measured in 17 participants, yielding an inter-observer variability of 5.0% (±SD 4.0%). At a second occasion, including 13 participants, the inter-observer variability was 7.2% (±SD 9.9%). The main exclusion criterion for c-f PWV assessment was atrial fibrillation.

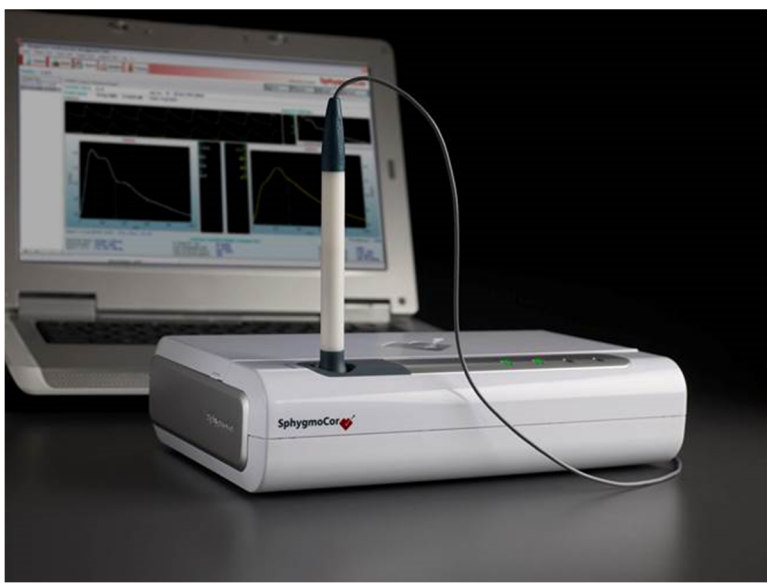

Figure 2.
This device (SphygmoCor®) was used for the assessment of c-f PWV and central BP in the MDC-CV reexamination.

Central BP (Paper II)

The SphygmoCor® device was used also for the assessment of central BP by means of pulse wave analysis. The radial artery pressure waveform was obtained with a pressure sensitive probe. After calibration with brachial BP, the aortic pressure waveform was estimated by a validated generalized transfer function [157]. Central BP components were generated from this waveform. PP amplification was calculated as brachial PP divided by central PP.

Copeptin (Paper III)

Fasting plasma samples from the MPP reexamination had been stored at -80°C. Copeptin was measured in these plasma samples with a commercially available assay in the chemiluminescence/coated tube format (B.R.A.H.M.S. AG, Henningsdorf, Germany) [199].

3.4 Cognitive tests

Using standard procedures, trained interviewers administered the cognitive tests in the MDC-CV reexamination. For 95% of the participants, arterial stiffness and cognitive function were measured on the same day.

MMSE (Paper I, II, IV)

The Mini-Mental State Examination (MMSE) is a widely used test of global cognitive function [218]. MMSE tests orientation, calculation, attention, verbal recall, expressive language, and visual construction. The maximal total score is 30 points, and the results are influenced by age and educational level [219]. The test-retest reliability has generally been reported to be good [219].

AQT (Paper I, II, IV)

AQT is a test of perceptual and cognitive speed, including set shifting, attention, and working memory [220] (Figure 3). In parts one and two of the test, the time it takes to name the color (red, black, yellow, or blue) of 40 squares, and to name the shape (circle, square, rectangle, or triangle) of 40 geometric figures is measured. In part three, which is the most difficult part, the time it takes to name both the color

and the shape is measured. AQT has good test-retest reliability [220, 221], and proven validity for detection of early dementia [222, 223]. AQT is used in clinical practice as a routine cognitive screening test in southern Sweden. In line with most other studies including AQT testing, only data from AQT part three were analyzed in the studies of this thesis.

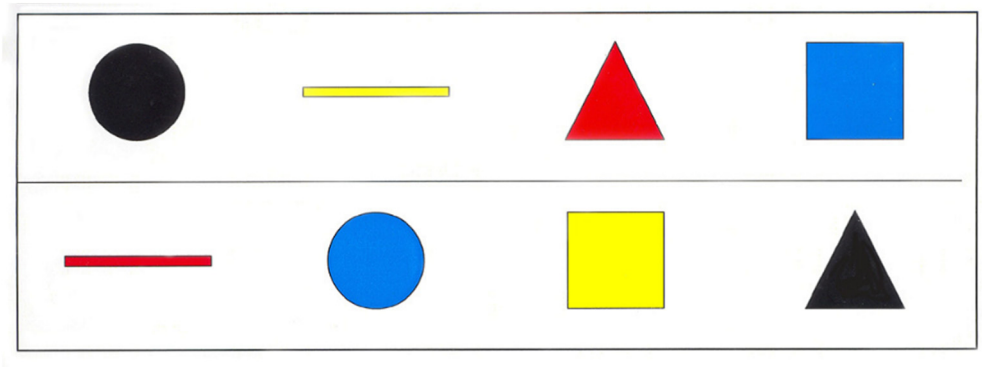

Figure 3.
A sample of AQT part three.

3.5 Ascertainment of dementia diagnoses

Cases of incident dementia (Papers III and IV) were identified by linkage with the Swedish National Patient Register (SNPR). This register is operated by the National Board of Health and Welfare (Socialstyrelsen), and covers more than 99% of all hospital discharge diagnoses, as well as diagnoses from hospital-based outpatient care [224]. The diagnoses are coded according to ICD, and all dementia diagnoses up until 31 December 2009 (Paper III), and 31 December 2014 (Paper IV), were retrieved. Thereafter, the diagnoses were validated by using information from medical records, and laboratory and neuroimaging data, when available. The final diagnosis was adjudicated by a research physician and a geriatrician specialized in memory disorders.

In Paper III, all-cause dementia was diagnosed according to the criteria of DSM-IIIR [225]. When Paper IV was drafted, DSM-5 [14] had been published, and was hence used as diagnostic criteria for all-cause dementia, AD dementia, and VaD. The DSM-IV criteria [19] were applied for the AD dementia and VaD diagnoses in Paper III. The diagnosis of mixed dementia was used when the patient had a clinical presentation and neuroimaging findings suggesting that both Alzheimer and cerebrovascular pathology significantly contributed to the disorder.

In Paper IV a complementary source was used to identify cases of prevalent dementia. Participants in the MDC-CV reexamination scoring below pre-set cut-offs on the cognitive screening tests (MMSE ≤ 24 points, AQT part three >90 seconds) were invited to a thorough clinical investigation at the Memory Clinic, Malmö, and participants with prevalent dementia were identified. The median time elapsed between the cognitive testing in the MDC-CV reexamination and the first visit at the Memory Clinic was 95 days.

3.6 Statistics

All analyses were performed in SPSS versions 20.0 and 22.0 (SPSS Inc., Chicago, Illinois, USA). A two-sided *P*-value of less than 0.05 was considered statistically significant.

Crude differences between groups were tested with the independent samples *t*-test, analysis of variance (ANOVA), the Mann Whitney test, and chi-square tests, as appropriate.

Associations between predictors (c-f PWV, BP components, copeptin) and outcomes (cognitive test results, dementia diagnoses) were assessed with multivariable adjusted regression models. Linear regressions were used for continuous, and logistic regressions for dichotomous dependent variables. Logistic regressions were used rather than Cox regressions because the time of onset of dementia could not be measured with accuracy. Analyses were conducted to ensure no violation of the assumptions underlying the regression models. Collinearity between the independent variables was present in Paper II, and therefore the different BP components were entered separately. In all four papers, statistical methods allowing for nonlinear associations were also used. This was achieved by dividing the predictor variable into quartiles (Papers III and IV), dichotomizing the predictor variable (Papers I and IV), and using quadratic and cubic terms (Paper II).

Selection of covariates were based on previous literature, i.e., on theoretical, not statistical grounds [162, 171]. Adjustments were made in three steps. First, the crude association between predictor and outcome was assessed. Then, adjustment was made for demographic data (age, sex, and educational level – *Model 1*). Finally, in order to assess if the predictor had added value beyond traditional CV risk factors, further adjustment was made for them (*Model 2*). Because MAP, heart rate, and height directly affect c-f PWV level [226, 227], adjustment should be made for these factors when c-f PWV is the predictor of interest (Papers I and IV). This explains the minor differences that exist between the papers regarding the selection of covariates.

3.7 Ethics

All participants in the studies of this thesis signed an informed consent. The studies were all approved by the Ethical Committee of Lund University, Lund, Sweden.

4 Main results

The main results of the four papers are presented below. The papers in their entirety, including detailed information about the study populations, the covariates, and secondary and sensitivity analyses, are found in the Appendix.

4.1 Paper I

- After adjusting for demographics and traditional CV risk factors, a linear association was found between higher c-f PWV and worse results on AQT, but not between c-f PWV and results on MMSE (Table 5a).

Table 5a.
Association between c-f PWV (continuous) and cognitive test scores using linear regressions.

	Model 1				*Model 2*			
	AQT		**MMSE**		**AQT**		**MMSE**	
	B	***P*-value**	**B**	***P*-value**	**B**	***P*-value**	**B**	***P*-value**
c-f PWV	0.51	0.001	-0.028	0.055	0.37	0.039	-0.006	0.70

Effects are shown as unstandardized regression coefficients (B). *Model 1:* adjusted for age, sex, and education level. *Model 2:* further adjusted for MAP, heart rate, smoking status, total serum cholesterol, height, weight, diabetes status, BP-lowering drugs, and lipid-lowering drugs. High scores on MMSE denote better performance, high scores on AQT denote worse performance.

- Based on the hypothesis that individuals with very stiff arteries have a worse cognitive function than can be inferred from a linear association, the continuous c-f PWV measure was dichotomized at the 90th percentile (the binary variable denoted c- f PWV > 13.8). Given the pronounced cognitive reserve of the human brain, this hypothesis seemed biologically plausible, and was therefore tested. When c- f PWV > 13.8 was added to the regression models, the linear association between continuous c-f PWV and AQT disappeared, but c-f PWV > 13.8 was highly significant (Table 5b). The effect size (the unstandardized regression coefficient) indicates that the participants with very stiff arteries were 4 to 5 seconds slower completing AQT compared to the rest of the study population, adjusted for covariates.

C-f PWV > 13.8 also reached statistical significance when added to the regression model with MMSE as outcome variable.

Table 5b.
Association between c-f PWV (continuous and dichotomized) and cognitive test scores using linear regressions.

	Model 1				*Model 2*			
	AQT		**MMSE**		**AQT**		**MMSE**	
	B	***P*-value**	**B**	***P*-value**	**B**	***P*-value**	**B**	***P*-value**
c-f PWV	0.13	0.55	-0.001	0.98	-0.08	0.72	0.029	0.19
c-f PWV > 13.8	4.24	0.01	-0.30	0.046	4.81	0.004	-0.37	0.016

Effects are shown as unstandardized regression coefficients (B). *Model 1:* adjusted for age, sex, and education level. *Model 2:* further adjusted for MAP, heart rate, smoking status, total serum cholesterol, height, weight, diabetes status, BP-lowering drugs, and lipid-lowering drugs. High scores on MMSE denote better performance, high scores on AQT denote worse performance.

- The regression coefficients of all the covariates included in the multivariable linear regressions were not published in Paper I. Since this information may be of interest, it is presented in Table 6. As can be seen, age and education were the covariates with the strongest association with the cognitive test results. The proportions of the variance in the cognitive test scores explained by the independent variables were quite low (model $R^2 = \sim 0.10$).

Table 6.
Linear regressions with cognitive test results (AQT and MMSE) as dependent variables.

	AQT			MMSE		
	B	**β**	***P*-value**	**B**	**β**	***P*-value**
Age, years	0.65	0.19	0.000	-0.06	-0.18	0.000
Male sex	2.97	0.08	0.008	-0.49	-0.14	0.000
Educational level						
9-10 vs ≤8 years	-4.85	-0.12	0.000	0.45	0.12	0.000
11-12 vs ≤8 years	-5.60	-0.09	0.000	0.70	0.12	0.000
≥13 vs ≤8 years	-6.12	-0.13	0.000	0.82	0.20	0.000
Diabetes	1.84	0.03	0.097	-0.17	-0.03	0.10
Total cholesterol, mmol/l	-0.93	-0.05	0.024	-0.02	-0.01	0.65
Current or former smoker	-0.13	0.00	0.86	0.02	0.01	0.75
Weight, kg	0.02	0.02	0.49	0.00	-0.03	0.28
Height, cm	-0.16	-0.08	0.012	0.03	0.14	0.000
Mean arterial pressure, mmHg	0.07	0.04	0.075	0.00	-0.01	0.69
Heart rate, beats/min	0.00	0.00	0.93	-0.01	-0.07	0.000
BP-lowering drugs	0.42	0.01	0.60	-0.03	-0.01	0.65
Lipid-lowering drugs	-2.27	-0.06	0.016	-0.05	-0.01	0.54
c-f PWV, m/s	0.37	0.05	0.039	-0.01	-0.01	0.70

All covariates in *Model 2* entered as independent variables. B is the unstandardized regression coefficient and β is the standardized regression coefficient. High scores on MMSE denote better performance, high scores on AQT denote worse performance.

4.2 Paper II

- Cross-sectionally at the reexamination, higher BP levels (systolic, diastolic, as well as PP) were significantly associated with worse results on both cognitive tests (AQT and MMSE) after full adjustment (Table 7). The effect sizes were small, and the addition of the BP variables to the regression models did not change R^2 substantially.

Table 7.
Linear regressions showing the association between BP components and cognitive test results.

		Model 1				*Model 2*			
		AQT		MMSE		AQT		MMSE	
		β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
Baseline									
Brachial	Systolic BP	0.03	0.1	-0.04	0.04*	0.02	0.4	-0.02	0.2
	Diastolic BP	0.03	0.2	-0.04	0.02*	0.02	0.3	-0.04	0.09
	PP	0.02	0.3	-0.02	0.2	0.01	0.7	-0.01	0.7
Reexamination									
Brachial	Systolic BP	0.06	<0.01*	-0.06	<0.01*	0.06	<0.01*	-0.05	0.01*
	Diastolic BP	0.04	0.03*	-0.04	0.02*	0.05	0.01*	-0.05	0.02*
	PP	0.06	<0.01*	-0.05	0.01*	0.05	0.02*	-0.04	0.04*
Central	Systolic BP	0.06	<0.01*	-0.05	0.02*	0.06	<0.01*	-0.04	0.03*
	Diastolic BP	0.04	0.03*	-0.05	0.02*	0.05	0.01*	-0.05	0.02*
	PP	0.05	0.01*	-0.03	0.12	0.05	0.01*	-0.03	0.2

Effects are shown as standardized regression coefficients (β). *Model 1:* adjusted for age, sex, and education level. *Model 2:* further adjusted for smoking status, total serum cholesterol, BMI, diabetes status, and BP-lowering drugs. The BP components were individually entered into the models. High scores on MMSE denote better performance, high scores on AQT denote worse performance. * denotes $P < 0.05$.

- Prospectively, no adjusted association was found between BP measured at the baseline examination and cognitive test scores at the reexamination 17 years later (Table 7).
- By reporting standardized regression coefficients, direct comparisons could be made between the different BP components. Central BP was not more strongly associated with the cognitive outcome than brachial BP (Table 7). In line with this, there was no association between the PP amplification and cognitive function.
- The use of BP-lowering drugs increased from 14.4% at baseline to 47.6% at the reexamination. After stratification, significant associations between BP and cognition were mainly found in the group taking BP-lowering drugs at the reexamination.

4.3 Paper III

- During a median follow-up of 4.2 years, 374 cases of incident dementia were identified. Of these cases, 120 were classified as AD dementia, 84 as VaD, and 102 as mixed dementia.
- After adjustment for demographics, traditional CV risk factors, and prevalent stroke, baseline plasma copeptin predicted incident VaD, but not all-cause dementia, AD dementia, or mixed dementia (Table 8). Compared with individuals in the lowest quartile of copeptin, those in the top quartile had a 2.5-fold increased risk of incident VaD.

Table 8.
Baseline plasma copeptin in relation to incident dementia during follow-up.

	Model 1		***Model 2***	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
All-cause dementia	1.03 (0.92-1.15)	0.61	1.05 (0.94-1.18)	0.40
AD dementia	0.92 (0.76-1.12)	0.43	0.97 (0.79-1.18)	0.74
VaD	1.41 (1.12-1.77)	0.003	1.30 (1.03-1.64)	0.03
Mixed dementia	0.81 (0.66-1.00)	0.05	0.85 (0.68-1.05)	0.13

Effects are shown as multivariable-adjusted odds ratios (OR) per 1 SD increase in log copeptin. *Model 1:* adjusted for age, sex, and education level. *Model 2:* further adjusted for systolic BP, BMI, LDL, HDL, current smoking, anti-hypertensive treatment, prevalent diabetes, and prevalent stroke.

- Notably, *lower* levels of some of the traditional CV risk factors (systolic BP, BMI, LDL cholesterol) conferred a *higher* risk of dementia during follow-up, i.e., an inverse association (Table 9).
- In order to examine the relationship between copeptin and the other covariates studied, a linear regression was performed with log copeptin as the dependent variable and all the other covariates in *Model 2* as independent variables. Copeptin was significantly and independently associated with most other markers of CV risk.

Table 9.
All significant covariates ($P < 0.05$) in logistic regressions with incident dementia as dependent variable.

	All-cause dementia	AD dementia	VaD	Mixed dementia
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age, per year	1.14 (1.11-1.16)	1.13 (1.09-1.17)	1.13 (1.08-1.18)	1.15 (1.10-1.19)
Female sex	2.00 (1.53-2.60)	3.02 (1.93-4.72)		
Systolic BP, per mmHg	0.99 (0.98-1.00)			
BMI, per kg/m^2	0.92 (0.89-0.95)	0.91 (0.86-0.97)		0.85 (0.80-0.91)
Current smoking		0.42 (0.22-0.81)		
LDL, per mmol/l			0.72 (0.55-0.94)	
Prevalent stroke			2.69 (1.39-5.23)	
Log copeptin, per 1 SD			1.30 (1.03-1.64)	

Entered independent variables: age, sex, education level, log copeptin, systolic BP, BMI, LDL, HDL, current smoking, anti-hypertensive treatment, prevalent diabetes, and prevalent stroke.

4.4 Paper IV

- There were 57 prevalent dementia cases at baseline (23 AD dementia, 3 VaD, 22 mixed dementia), and 102 incident cases (30 AD dementia, 17 VaD, 42 mixed dementia) were identified during a median follow-up of 4.6 years.
- In unadjusted logistic regressions, c-f PWV was associated with prevalent as well as with incident all-cause dementia, but the associations disappeared after adjustment for other covariates. Similarly, in analyses of covariance (ANCOVA), adjusted for age, sex, and education level, mean c-f PWV was not higher in the prevalent and incident dementia cases, compared with the rest of the study population (Figure 4). C-f PWV was not significantly associated with prevalent or incident dementia subtypes (AD dementia, VaD, mixed dementia), but these results must be interpreted in the context of wide confidence intervals.
- When Cox regressions were used instead of logistic regressions, the hazard ratios for c-f PWV were almost identical to the odds ratios from the logistic regressions, probably due to the relatively small number of dementia cases, limited follow-up time, and low drop-out rates.

- In the multivariable model, the traditional CV risk factors were not significantly associated with the dementia outcomes with one exception: *lower* weight at baseline conferred a *higher* risk of dementia during follow-up.

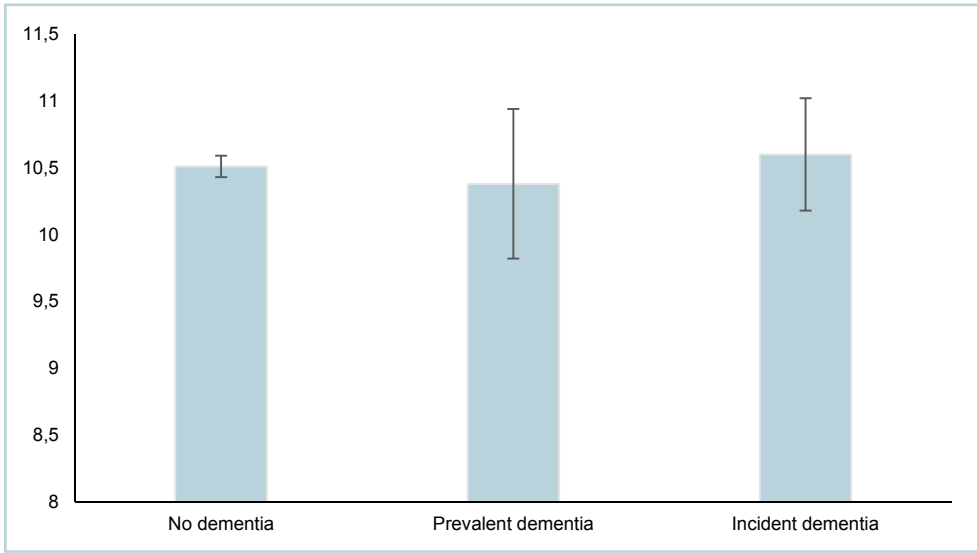

Figure 4.
Adjusted means of c-f PWV (m/s) with 95% confidence intervals in subgroups with or without dementia. Adjusted for age, sex, and education level.

5 Discussion

5.1 Traditional CV risk factors

In Papers III and IV, *lower* baseline levels of some of the traditional CV risk factors (systolic BP, BMI, and LDL cholesterol in Paper III; weight in Paper IV) were associated with a *higher* risk of dementia during follow-up, i.e., inverse associations. This might seem counterintuitive since these are all well-known risk factors for dementia. However, as pointed out in the Introduction, this is true mainly when they are measured in midlife, not in late-life. Several mechanisms may explain the observed inverse associations (Figure 5). *First*, it is well known that demented individuals lose weight and that their BP decreases [3, 44]. We had rather short follow-up times, and the dementing process in the brain had probably already started when the covariates were measured. Therefore, a reverse causation (i.e., the cognitive disorder affecting the covariates and not vice versa) seems plausible. *Second*, a common underlying factor might have affected both the dementia risk and the levels of the CV risk factors. For example, the presence of physical frailty has been shown to have these effects [128, 129, 228]. *Third*, low BP might *per se* cause cerebral hypoperfusion and dementia [229], but this explanation is not applicable to the other traditional CV risk factors.

In Paper II, higher brachial BP was cross-sectionally associated with worse results on the cognitive tests, but BP at the MDC baseline examination did not predict cognitive test results 17 years later. The results contradict the frequently held assumption that higher BP in midlife is a risk factor for late-life cognitive decline [83, 94, 230]. It should be noted, though, that cognitive function was only measured once in the MDC study, and conclusions about cognitive decline over time could therefore not be drawn. It should also be noted that there are an abundance of studies on the relationship between BP and cognition, and the results of these studies have been very inconsistent [83, 94]. However, the apparently heterogeneous results appear more similar if the generally small effect sizes and the differences in study designs are considered. In Papers I and II, the association of cognitive function with BP was weak in relation to the association of cognitive function with age and educational level.

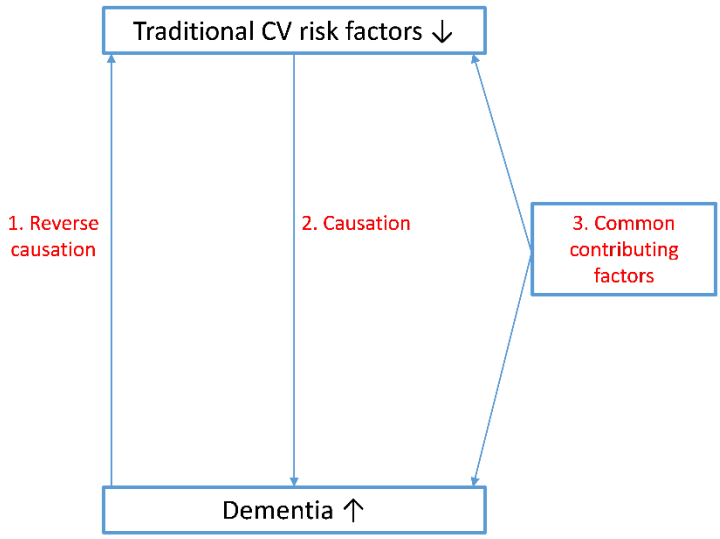

Figure 5.
Mechanisms that may explain the observed association between traditional CV risk factors and dementia risk in our studies with elderly populations and short follow-up times.

In Paper II, the inverse cross-sectional association between BP and cognitive performance was mainly seen in the group taking BP-lowering drugs, but use of BP-lowering drugs was not by itself associated with cognitive test results in multivariable regressions (Tables 6 and 7). Some, but not all, other observational studies have found that use of antihypertensive medications, and in particular some therapeutic classes such as the angiotensin-receptor blockers (ARBs), decreases the risk of cognitive decline and dementia [83, 94, 231]. This is in line with the conclusions drawn in a recent large Mendelian randomization study: Ostergaard *et al.* found that genetically predicted higher systolic BP was associated with a lower risk of AD dementia [232]. Since the individuals with inherited lifetime exposure to higher systolic BP also were using more antihypertensive medications, the authors speculated that these medications caused the decreased AD dementia risk. This highlights the complexity and potential bias that is introduced when a large proportion of the study population is under treatment with medications affecting the CV system. In the studies included in this thesis, this proportion was almost 50%.

5.2 c-f PWV

In Paper I, a higher c-f PWV was associated with worse results on the cognitive tests, independently of traditional CV risk factors. Consequently, c-f PWV had added value over and above the traditional CV risk factors. The findings are broadly in line with previous research in the field, and could have several hypothetical explanations (Figure 6). *First*, stiff arteries cause transmission of flow pulsations into the passively perfused brain, damaging small fragile vessels [139, 173, 233]. In line with that, c-f PWV has been related to radiologic markers of cerebral small-vessel disease [162]. Such small-vessel disease primarily affects subcortical regions of the brain, with resultant decline in processing speed and executive function [28, 49]. This possibly explains why c-f PWV was primarily associated with AQT, a measure of cognitive speed. *Second*, the observed association might be caused by cerebral hypoperfusion. As a result of the cross-talk between large and small arteries, stiffness of the large elastic arteries is associated with arteriolosclerosis and a reduced diameter in the small arteries of the brain [134, 234]. This might result in downstream hypoperfusion, possibly manifesting as WMH and cognitive decline [235]. *Third*, the observed association might not be causal but merely a reflection of common underlying factors. We and others have adjusted for potential confounders, but rest confounding might be present. For example, the biological ageing process *per se* might be associated with both vascular and cognitive ageing [236]. If this was the case, c-f PWV could still be an interesting risk marker for cognitive decline, even though it is not causally related to it.

In Paper I, the linear association between continuous c-f PWV and AQT results reached statistical significance. However, when other statistical techniques were used, the association could be explained by individuals in the top decile of c-f PWV. This underlines the importance of using statistical methods that account for non-linear associations. Similar to the results of Paper I, two recent publications have reported non-linear associations between c-f PWV and cognitive test results: Tsao *et al.* found that individuals in the fifth quintile of c-f PWV had the greatest cognitive decline [177], and Scuteri *et al.* reported that individuals in the top quartile of c-f PWV had a four-fold increased risk of becoming cognitively impaired during follow-up [186]. Given that the brain has a remarkable reserve capacity [78, 79], one interpretation of the results could be that only very stiff arteries confer negative effects on cognition. However, such interpretations must be stated with caution, since both random and systematic errors might affect them.

In Paper IV, no independent association was found between c-f PWV and prevalent or incident dementia. Although some recent reviews have assumed that such an association exists [169, 170], our findings are in line with previous research [176, 193]. In conclusion, our MDC study, as well as other large population-based studies,

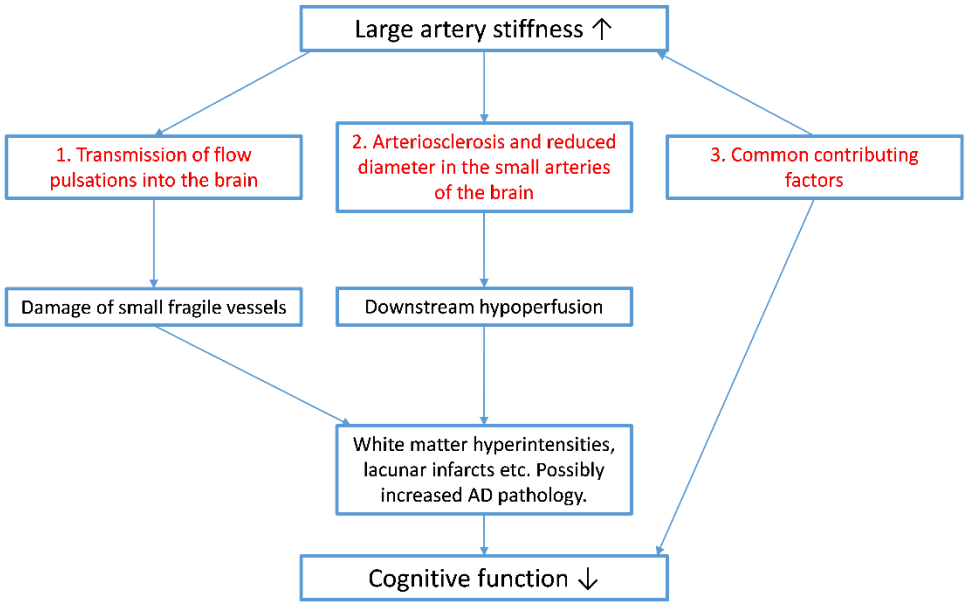

Figure 6.
Mechanisms that may explain the association between c-f PWV, as a measure of arterial stiffness, and cognitive decline.

have found associations between c-f PWV and cognitive test results, but not between c-f PWV and risk of dementia. What could be the explanation for these seemingly counterintuitive findings (Figure 7)? *First*, it could be a power issue. The linear regressions with cognitive test results as the dependent variable, where thousands of individuals have been contributing data, could in the majority of the studies detect an association, but the dementia cases in the Cox or logistic regressions might have been too few. The power issue is even more important to consider when dementia subtypes, such as VaD, is the outcome under study. *Second*, the reverse causation discussed above in the context of traditional CV risk factors might be applicable also to c-f PWV, even though no studies to date have provided any evidence of the existence of such an effect. *Third*, as pointed out in the Introduction, a poor result on cognitive testing represents something very different than a diagnosis of dementia. Dementia is in most cases qualitatively different from the normal ageing process, not just representing the upper end of a continuum with it [16, 74]. Therefore, cognitive test results in population-based studies primarily reflect normal cognitive ageing, not dementia (given that 'normal cognitive aging' is defined to include some pathological conditions but not dementia). C-f PWV, as an indicator of vascular ageing, might be more closely related to a slightly increased rate of age-related cognitive decline, than to a diagnosis of dementia. Notably, the cognitive domains that in most studies have been associated with c-f PWV

(attention, executive function, cognitive speed, memory), are also the domains that primarily deteriorate with age [17]. It is also interesting to note that some of the other CV risk factors had *different* associations with cognitive test results, compared with their associations with dementia. For example, weight measured at the MDC-CV reexamination was not at all associated with cognitive test results (Paper II), but it was inversely associated with dementia risk (Paper IV). Likewise, BP was associated with cognitive test results (Paper II) but not with dementia (Paper IV). These examples are of course very speculative, since the association with cognitive test results was cross-sectional, and the association with dementia was cross-sectional as well as prospective. However, the examples corroborate the notion that cognitive test results in the general population should not be used as a surrogate marker for dementia.

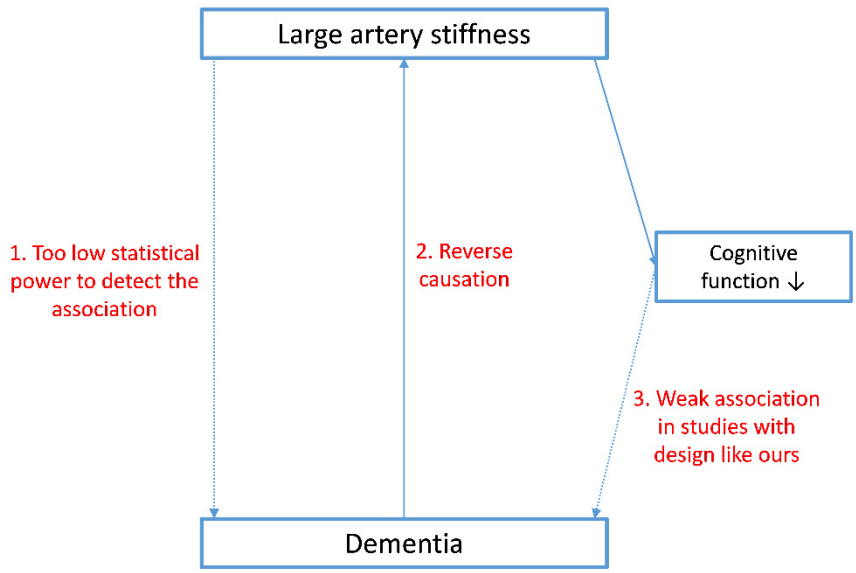

Figure 7.
Factors that may explain our observed lack of association between c-f PWV, as a measure of arterial stiffness, and dementia risk.

5.3 Central BP

In Paper II, central BP was not more closely associated with the cognitive test results than brachial BP was. If this finding reflects the truth, central BP is not a better marker than brachial BP in this regard. Our result contradicts the only previous study that has been reporting on this issue [195], but their study population was small, and composed of young, healthy volunteers. As discussed in recent papers, brachial and central BP are very highly correlated [153, 194]. This, and the fact that the coefficient of variation of central BP is similar to that of brachial BP, makes it difficult on statistical grounds to detect a difference on the outcome of interest between the two of them.

Another possibility is that our null finding merely reflects methodological problems. The ability of the SphygmoCor® device to correctly estimate central BP has been questioned [237, 238], even though validation studies have been conducted [158]. For example, the generalized transfer function used has been derived from pulse wave analysis in selected patient groups, and might not be applicable to the general population. However, neither in population-based studies, nor in the clinical setting, is it possible to invasively measure central BP on a routine basis. A certain degree of inaccuracy is therefore inevitable, and SphygmoCor® is currently the most commonly used device for noninvasive estimation of central BP [238].

5.4 Copeptin

In Paper III, the baseline plasma copeptin level predicted VaD but not AD dementia, independently of traditional CV risk factors. Even though the study does not address the question of clinical utility of measuring copeptin in patients with cognitive complaints, two important conclusions can be drawn. *First*, since higher level of copeptin was related to an increased risk of VaD, the association does not seem to be affected by the reverse causation discussed above. *Second*, copeptin seems to be selectively associated with VaD, not with AD dementia. Since many of the vascular risk factors/markers have been shown to increase the risk not only of VaD, but also of AD dementia [49, 53-55], it would be valuable to find risk markers that are more selectively associated with VaD. Our study is the first to report on the association between copeptin and dementia, and further studies are needed for confirmation.

Several pathophysiological hypotheses linking a higher copeptin level with an increased risk of VaD can be formulated (Figure 8). Copeptin has been associated with diabetes mellitus and impaired glucose metabolism [201, 202], which are well-recognized risk factors for dementia, in particular VaD [9, 115]. Copeptin has also

been found to be higher in individuals with prevalent CV diseases [204], for example heart failure and stroke. In Paper III, copeptin was independently associated with most other markers of CV risk in linear regressions with log copeptin as the dependent variable. Furthermore, the level of copeptin predicts the prognosis in many CVDs [200, 208, 209], and it thus seems to be a marker of disease severity and risk. In this context, our finding that copeptin predicts VaD seems plausible. Finally, the fact that vasopressin acts locally as a neuropeptide in the brain is intriguing. Neuropeptides can both affect and be affected by neurodegenerative processes, and vasopressin has been suggested to be involved in learning and memory processing in healthy individuals [197]. However, only a very small fraction of vasopressin crosses the blood-brain barrier [198], so the levels of peripheral copeptin that we have measured do not reflect vasopressin levels in the brain.

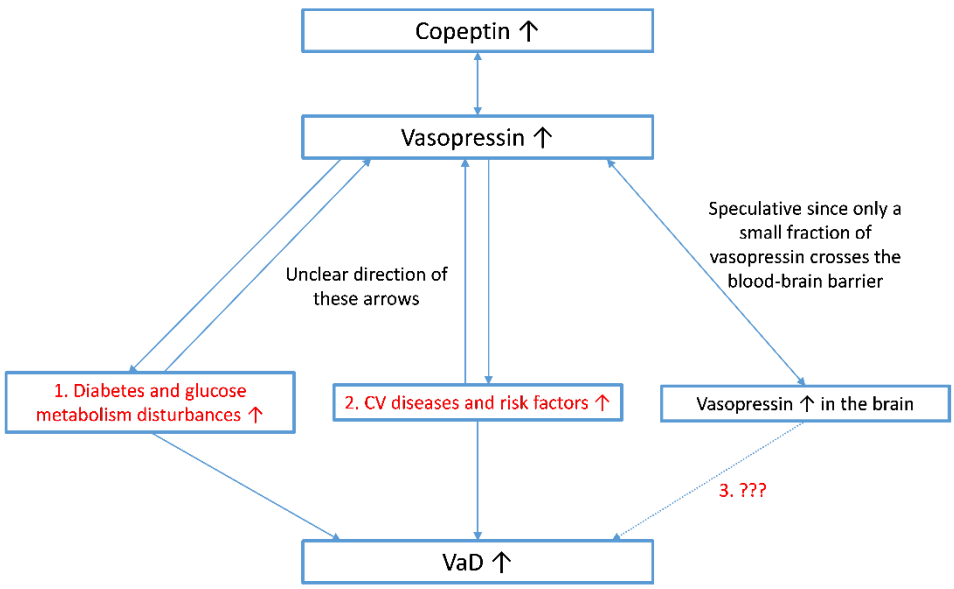

Figure 8.
Mechanisms that may explain our observed association between plasma copeptin and VaD risk.

5.5 Dementia as outcome

In Papers III and IV, the SNPR was used to identify cases of incident dementia. This strategy most certainly underestimated the true incidence rates in at least two ways. *First*, the SNPR only includes information from hospital-based care [224]. Hence, patients treated only in primary care are not covered. *Second*, a substantial proportion of individuals suffering from dementia does not have a dementia diagnosis at all [239], and are consequently not registered in the SNPR. The magnitude of the underestimation of the true incidence and prevalence can only be a matter of speculation. Two small Swedish studies have tried to answer this question [240, 241], and they found the sensitivity of the SNPR regarding identification of dementia cases to be 23% to 55%.

We applied a thorough validation process to overcome validity problems regarding the diagnoses in the SNPR. In observational studies, it is very important that the clinical subtypes of dementia are correctly diagnosed, in order to infer conclusions about risk prediction. Suppose, for example, that a potential risk marker is *not* associated with AD dementia. If the presence of this risk marker (it could be, for example, BP or hypercholesterolemia) in a patient increases the likelihood that the clinician will diagnose the patient with VaD – then it will incorrectly look like the risk marker has an inverse association with AD dementia.

Another important issue to consider when studying dementia is whether dementia in an otherwise relatively healthy person is the same as dementia in a frail, multimorbid person. Probably not. And still, dementia (also in this thesis) is usually only categorized based on presumed pathology, not based on the phase of life the patient is in. Dementia that afflicts an otherwise healthy individual can be considered mainly a neurological disorder. But in a frail, multimorbid individual in the phase of 'terminal cognitive decline' [242, 243], it is probably more appropriate to consider it a geriatric disorder. These two disorders probably have very different risk factors, different prognoses, and require different treatments. Still, they are reduced into constructs such as VaD and Lewy body dementia. The studies included in this thesis were not designed to investigate this issue, but it should be considered in the planning phases of future studies.

Most individuals will become demented if they only live long enough. Therefore, genetic and environmental factors that are associated with longevity might paradoxically be associated with an increased risk of dementia. This is important to bear in mind when interpreting observational studies in the oldest old. The fact that these survival effects are complex can be illustrated by the association between diabetes and dementia. It has been shown in many observational studies that having diabetes increases the risk of future dementia [9, 115]. Does this mean that treating or even preventing diabetes would reduce dementia in the population? Possibly not,

since a reduction in the incidence of other diseases linked to diabetes, such as myocardial infarction, would increase longevity [80].

5.6 Publication bias

Publication bias occurs when the outcome of a study influences the decision whether to publish it or not. In other words, it occurs when publication depends not only on the quality of the research but also on the hypothesis tested, and the direction and statistical significance of the effects. There is robust evidence for the existence of publication bias [244], and studies with statistically significant results are more likely to be accepted for publication [245]. This leads to reporting bias (selective reporting of results) and HARKing ('Hypothesizing After the Results are Known') [246] – two widespread phenomena in epidemiological research. Further, it leads to type 1 statistical errors in meta-analyses and systematic reviews [247].

Thus, it is not surprising that Papers II and IV, which present mainly neutral results, were more cumbersome to get accepted for publication than Papers I and III. It is also not surprising that a recent review on the association between arterial stiffness and cognitive impairment concluded that publication bias probably exists in this area of research [162]. This conclusion was based on the observation that studies reporting a statistically significant effect were smaller compared with studies that did not find such an effect. Adhering to the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) [248] is one way to reduce publication bias. Another way is to require registration of the study protocols of observational studies in publicly accessible registers [249].

5.7 Representativity

Are the participants of the MPP and MDC studies representative of the population in Malmö, the city where the studies were conducted? Possibly, but some points need consideration. *First*, the MPP and MDC are historical cohorts. The demographics of a city change over time, just as the risk factor patterns. *Second*, the attrition from the studies was not random, and a health selection bias has occurred, with participants being healthier than non-participants [217, 250]. Most certainly, this applies both to CV and to cognitive disorders. It is well-known that people with cognitive impairment are less likely to participate in population-based studies [251], and they are more likely to be lost to follow-up [252]. This probably explains the high mean MMSE results (28.1 points) in the MDC-CV reexamination. Also,

participants who were excluded from the study populations of the papers in this thesis had more CVDs and risk factors compared with included individuals. For example, participants with atrial fibrillation were excluded from Papers I and IV because it was not possible to measure their c-f PWV.

Whether this health selection bias has affected our results or not can only be a matter of speculation. Since increased CV burden confers an increased risk of cognitive impairment and dementia, it might be assumed that the bias that this has introduced is towards null. Finally, it should be noted that representativity is not the same as generalizability. Even though a sample can be considered as representative of the target population, the results might not be generalizable to other populations.

6 Conclusions

Based on analyses in two population-based cohorts in Malmö, Sweden, the following conclusions were drawn:

- An inverse cross-sectional association was found between c-f PWV, a marker of arterial stiffness, and cognitive function, particularly cognitive speed. Since the results remained statistically significant after adjustment for demographics and traditional CV risk factors, c-f PWV provided added value over and above these factors. The relationship between c-f PWV and cognitive function was non-linear, with individuals in the top decile of c-f PWV explaining the association.
- Systolic, as well as diastolic, BP was inversely associated with cognitive function cross-sectionally, but not prospectively with BP measured 17 years before cognitive testing. Central BP did not show a stronger association with cognitive function than brachial BP. Significant associations were mainly found in the group taking BP-lowering drugs.
- Baseline plasma copeptin, a marker of vasopressin, predicted VaD, but not AD dementia, mixed dementia, or all-cause dementia, over 4.2 years of follow-up. The results remained statistically significant after adjustment for demographics and traditional CV risk factors.
- No independent cross-sectional association was found between c-f PWV and all-cause dementia or subtypes of dementia, and neither did c-f PWV predict incident dementia over 4.6 years of follow-up.
- Lower baseline levels of some of the traditional CV risk factors were associated with a higher risk of dementia during follow-up. This highlights that new vascular risk markers are needed in elderly patients with incipient cognitive decline.

7 Future perspectives

What is 'normal' cognitive ageing [80]? How can it be separated from 'pathological' cognitive ageing? How do these processes relate to MCI and dementia, and what factors are selectively associated with them? Are cerebrovascular changes seen on MRI of the brain always pathological, or are they part of the normal ageing process? Questions like these, at the intersection between geriatrics and gerontology, are interesting both from a theoretical and a clinical perspective.

Results from several population-based studies, including the research presented in this thesis, indicate that elderly individuals with stiff arteries are subject to a slightly increased rate of cognitive decline, but they do not have a markedly increased risk of dementia. Whether these findings reflect the truth, or whether they merely reflect biases and methodological shortcomings, remains an unresolved question. Future studies with dementia as outcome should preferably employ longer follow-up times to increase the number of dementia cases (i.e., increase the statistical power), and to rule out the possibility of a reverse causation. These analyses can be done within a few years in the existing population-based cohorts.

Arterial stiffness is modifiable, both pharmacologically and by lifestyle interventions. For example, exercise, weight loss, and certain BP-lowering drugs have all been shown to reduce c-f PWV [253-255]. To date, no intervention trials have investigated how modification of arterial stiffness affects cognitive performance [172]. Such trials would be very interesting, but limited by the short follow-up times as discussed below.

The associations between vascular factors on the one hand, and cognitive decline, AD, and VaD on the other hand, are complex and not fully understood. Since vascular factors exert their effect from childhood onward, a life-course approach to these associations should preferably be applied. Since observational studies cannot prove causality, and since randomized controlled trials usually have too short durations in this perspective, other methods will be needed. Mendelian randomization is one such method for indicating causality [256].

In this thesis, vascular biomarkers were analyzed to elucidate disease mechanisms and causes at the population level. This approach is theoretical and cannot easily be extrapolated down to the individual patient level. From a clinical perspective, it would be of great value to identify vascular biomarkers that can be used as

diagnostic and prognostic tools in the clinical setting. Further, future research should focus on how the clinician ideally should treat the traditional CV risk factors in patients seeking medical attention for incipient cognitive decline, and in patients with radiological evidence of cerebrovascular disease. By creating large, international consortiums, the power and the generalizability of the included studies can be increased [257, 258].

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