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CARDIOVASCULAR DISEASE IN DEMENTIA

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Cardiovascular disease in dementia

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

The objective of this thesis was to characterize the burden of cardiovascular diseases in patients with dementia, their treatment and association with survival. Further, we aimed to explore whether cardiac structure in young adults can affect the aging brain. We performed 5 observational cohort studies, based on patients registered in the Swedish Dementia Registry (Papers I-IV) and participants in a population-based study Coronary Artery Risk Development in Young Adults (Paper V).

The results can be summarized as follows:

(I) Seventy per cent of patients with dementia are prescribed cardiovascular drugs. Their use is highest in patients with vascular dementia and lowest in patients with Parkinson´s disease dementia.

(II) Patients with heart failure and dementia constitute an old and under-diagnosed population. Heart failure with preserved ejection fraction is the most common type of heart failure and vascular dementia the most frequent dementia disorder.

(III) The most common chronic cardiovascular disease in patients with dementia is ischemic heart disease (23% of patients are affected), followed by cerebrovascular diseases (20% of patients) and atrial fibrillation (19% of patients). The occurrence and prognostic significant of chronic cardiovascular diseases differs in specific dementia disorders.

(IV) Twenty one per cent of patients with dementia are managed invasively for acute myocardial infarction. The use of invasive procedures is associated with lower age and higher cognitive status. This study suggests that the invasive management of myocardial infarction has a benefit for survival of patients with dementia.

(V) Higher left atrial volume in young adulthood is associated with lower white matter integrity in mid-life. This study suggests that improvement of cardiac function in young adults may benefit the aging brain.

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I. **Cermakova P**, Fereshtehnejad SM, Johnell K, Winblad B, Eriksdotter M, Religa D. Cardiovascular medication burden in dementia disorders: a nationwide study of 19,743 dementia patients in the Swedish Dementia Registry.
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II. **Cermakova P**, Lund LH, Fereshtehnejad SM, Johnell K, Winblad B, Dahlström U, Eriksdotter M, Religa D. Heart failure and dementia: survival in relation to types of heart failure and different dementia disorders.
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Journal of American Director´s Association 2016, in press

V. **Cermakova P,** Muller M, Armstrong AC, Religa D, Bryan NR, Lima JA, Launer LJ. Cardiac parameters in young adults and their brain health in mid-life: CARDIA Brain MRI Sub-study.
Manuscript

LIST OF SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

I. Garcia-Ptacek S, Faxén-Irving G, **Cermakova P**, Eriksdotter M, Religa D. Body mass index in dementia.
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II. Fereshtehnejad SM, Damangir S, **Cermakova P**, Aarsland D, Eriksdotter M, Religa D. Comorbidity profile in dementia with Lewy bodies versus Alzheimer's disease: a linkage study between the Swedish Dementia Registry and the Swedish National Patient Registry.
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CONTENTS

LIST OF ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
AD	Alzheimer´s disease
CARDIA	Coronary Artery Risk Development in Young Adults
CI	Confidence interval
CVD	Cardiovascular disease
DLB	Dementia with Lewy bodies
DTI	Diffusion tensor imaging
FUS	Fused-in-sarcoma
FTD	Frontotemporal dementia
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD	International Classification of Diseases
MAPT	Microtubule-associated protein tau
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NSTEMI	Myocardial infarction without ST-elevation
OR	Odds ratio
PCI	Percutaneous coronary intervention
PDD	Parkinson´s disease dementia
SD	Standard deviation
STEMI	Myocardial infarction with ST-elevation
RAAS	Renin-angiotensin-aldosterone system
RiksSvikt	Swedish Heart Failure Registry
SveDem	Swedish Dementia Registry
TDP-43	TAR DNA-binding protein with molecular weight 43 kDa
VRF	Vascular risk factor

1 INTRODUCTION

The remarkable increase in life expectancy in developed countries is considered an accomplishment of the 20th century[1]. Resulting from better hygiene, the use of antibiotics and vaccinations, the risk of dying from infectious diseases has decreased substantially. Child and maternal mortality have rapidly dropped and people now reach mature age, when they face higher risks of chronic age-related conditions, such as cardiovascular disease (CVD) and dementia. Thanks to advances in medical care, many older people now survive several diseases that previously were fatal. As a consequence of this, older people are now able to tolerate a certain degree of disability, which we may understand as any health loss, other than death[2].

CVD, including a wide range of conditions, such as ischemic heart disease, cerebrovascular diseases, heart failure or cardiac arrhythmias, are leading causes of death worldwide[3]. Given major advancements in their prevention and therapy, the risk of dying from CVD was shifted to older ages. As opposed to declining trends of disability caused by CVD[4], a looming epidemic of dementia, the main cause of disability of the elderly patients, has brought concern[5]. Dementia is a heterogeneous syndrome constituted of several types (Table 1) and is characterized by progressive impairment in cognition that leads to patients´ dependency on caregivers. The prevalence of dementia increases with age, affecting 5% of the population over 65 years, and up to 50% of persons at the age of 90 years[6]. In 2015, almost 47 million people worldwide were estimated to be affected by dementia and this number is projected to reach 75 million by 2030[7].

Table 1 Types of dementia disorders[8-15]

Dementia disorder	Estimated proportion of all dementia cases
Alzheimer´s disease	50-70%
Vascular dementia	15%
Lewy body dementias	3-10% in population-based studies 20% in clinic-based studies
Frontotemporal dementia	1% among patients ≥ 68 years 3-26% among patients ≤ 65 years

1.1 DEMENTIA DISORDERS

1.1.1 Alzheimer´s disease

Alzheimer´s disease (AD) is the most common cause of dementia and accounts for two thirds of all cases[9]. Typically, AD starts with difficulties recalling recent events. As the disease progresses, patients start having problems with managing complex tasks, orientation and recognizing faces. Poor judgement, difficulties with language and behavioral and psychiatric symptoms also accompany AD (Figure 1)[9]. In atypical cases of AD, visual, executive and language problems are more pronounced and occur earlier than memory problems[16].

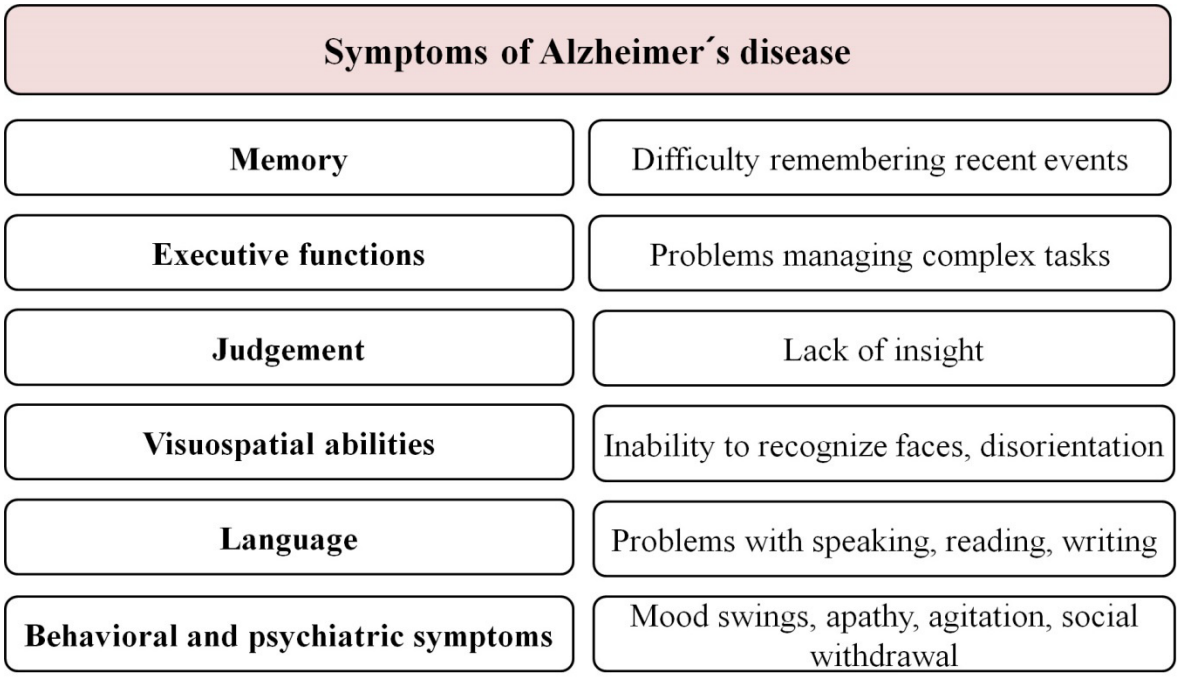

Figure 1 Clinical manifestation of AD[9]

AD usually affects people older than 65 years (late-onset AD), has a slow, progressive character and heterogeneous etiology. Several psychological, social and vascular risk factors for AD have been identified. The vascular risk factors are discussed in Chapter 1.2. The most important genetic risk factor is the presence of the ε*4* allele of the gene for apolipoprotein E (*APOE* ε*4*)[17]. In about 10% of patients, AD appears before the age of 65 (early-onset AD), often presents with atypical symptoms and is largely genetically determined[18].

Pathological hallmarks of AD include extracellular plaques of amyloid beta protein and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, together with degeneration of neurons and synapses. The amyloid cascade hypothesis postulated that amyloid deposition is the primary event that leads to the formation of tangles, degeneration of

neurons and dementia[19]. This hypothesis has been challenged by findings suggesting the occurrence of tangles before amyloid plaques, a correlation of cognitive decline with tangles, but not plaques, and an increase in amyloid as a consequence of neuronal damage caused by another process[20-22]. Moreover, amyloid depositions are frequent findings in the brains of persons who never had symptoms of dementia[23].

Most people with AD also have other pathologies in the brain, such as cerebrovascular lesions as well as findings primarily related to Lewy body dementias or frontotemporal dementia (FTD). They may contribute to the occurrence of the amyloid plaques and tangles or have an additive effect on them, lowering the threshold for the clinical presentation of dementia[24-26]. Several other hypotheses for AD have also been suggested, such as imbalance of the inflammatory system, energy metabolism, oxidative stress and dysregulation of the cell cycle[8,27].

The pathological processes in the brain may start up to decades before cognition declines and are reflected by biomarkers acquired from the cerebrospinal fluid and by neuroimaging methods[28]. The first detectable biomarkers are those of amyloid deposition and are followed by markers of neurodegeneration related to tau pathology, before cognitive impairment appears[29]. However, it is acknowledged that recognition of the earliest AD pathology is beneath the detection threshold of all currently used AD biomarkers[29]. Recent advances in sensitive magnetic resonance imaging (MRI) techniques are promising in detecting earlier stages of brain pathology. For example, diffusion tensor imaging (DTI) may reveal early disruption of integrity of white matter, years before other biomarkers become apparent[30,31].

Until now, there have been no disease-modifying treatments for AD and patients die within 4-7 years after the diagnosis[32-34]. Knowledge on the dysfunction of neurotransmitters led to the development of drugs that improve cognition, behavioral and functional status[35]. As degeneration of cholinergic neurons is an early event in AD, acetylcholinesterase inhibitors are the main therapy[35]. Co-administration of memantine, an N-methyl-D-aspartate receptor antagonist, further slows down cognitive and functional decline in patients with moderate-to-severe AD[35,36].

1.1.2 Vascular dementia

Vascular dementia is the second most common type of dementia disorder and accounts for around 15% of dementia cases[15]. It is characterized by cognitive impairment due to cerebrovascular lesions that vary in their number, location, form and size (Figure 2). Frequently present lesions in subcortical areas lead to deficits in attention, information

processing and executive functions[15]. Memory, language and praxis are variably affected and non-cognitive symptoms, in particular depression and apathy, often occur[15,37]. There is currently no treatment for vascular dementia. Mortality is higher than in AD, as it is estimated that patients die after 3-5 years since the diagnosis[15,38].

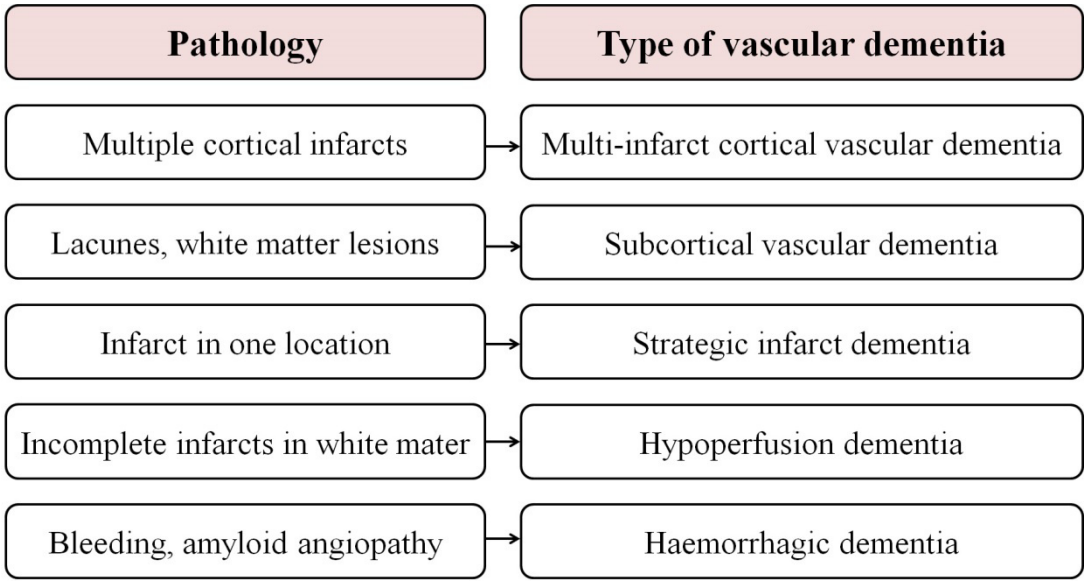

Figure 2 Types of vascular dementia due to different cerebrovascular lesions[15]

Individuals with vascular dementia are often afflicted with AD pathology and are then diagnosed with mixed dementia[39]. Mixed dementia is usually considered the third most common type of dementia, moving up to first or second rank among the oldest patients[40]. The threshold for distinguishing between AD and vascular dementia is unclear and depends on diagnostic traditions and resources[41,42]. Initially, mixed dementia was diagnosed in the presence of AD pathology and large infarcts. Later, the importance of lacunes and white matter lesions for cognitive impairment has become apparent. Thus, the diagnosis of mixed dementia covers a wide spectrum of combinations between AD pathology and vascular lesions[39-41].

1.1.3 Lewy body dementias

Lewy body dementias is an umbrella term for two clinical entities: dementia with Lewy bodies (DLB) and Parkinson´s disease dementia (PDD)[11]. It is characterized by the presence of dementia and motor symptoms of parkinsonism, such as tremor, rigidity and bradykinesia (Figure 3). The neuropathological hallmarks of Lewy body dementias are Lewy bodies and Lewy neurites that contain inclusions of alpha-synuclein, accompanied by degeneration of neurons[43,44].

Patients with DLB present with fluctuating cognitive impairment, recurrent visual hallucinations and rapid eye movement sleep behavior disorder. Parkinsonism occurs after or at the time of the manifestation of dementia in 60-90% of patients[45]. PDD is a clinical entity, in which dementia developed in an established Parkinson´s disease, at least 1 year after the onset of the motor symptoms[46]. The point-prevalence of dementia in Parkinson´s disease is 25%[47]. Whether the patients progress into dementia depends on their age and the duration of the disease. Ten years after the diagnosis of Parkinson´s disease, the risk of having dementia is 50%[11]. Once dementia manifests in Parkinson´s disease, no clinical difference can distinguish it from DLB.

Lewy bodies are found in several central and peripheral autonomic centers, leading to failure of parasympathetic and sympathetic nervous system[48]. Frequent manifestation of sympathetic dysfunction is orthostatic hypotension, present in 80% of patients with Lewy body dementias. Persistent orthostatic hypotension is a predictor of the survival of the patient[49]. Acetylcholinesterase inhibitors moderately benefit the patients with Lewy body dementias. Mortality is higher than in AD; the patients die on average 4 years after the diagnosis of dementia[38,50].

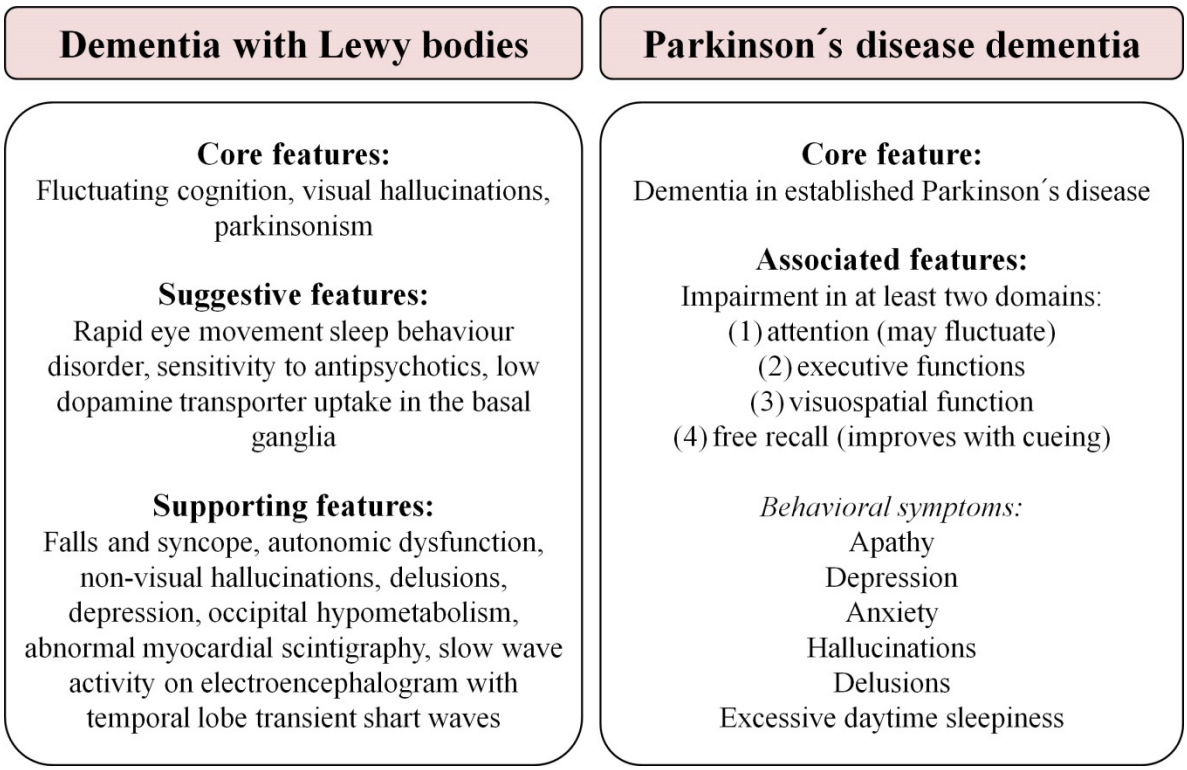

Figure 3 Features of Lewy body dementias[11]

1.1.4 Frontotemporal dementia

Frontotemporal dementia (FTD), the leading type of early-onset dementia, is characterized by neurodegeneration in frontal and temporal lobes. It can be classified as behavioral variant FTD, which presents with deficits in behavior and executive functions, or as primary progressive aphasia, where the main symptoms are problems with language (Figure 4)[13,51]. Features of motor neuron disease may occur in up to 40% of patients with FTD. Three main neuropathological hallmarks have been identified: microtubule-associated protein tau (MAPT), the TAR DNA-binding protein with molecular weight 43 kDa (TDP-43) and the fused-in-sarcoma (FUS) protein[52]. Family history of the disease is reported in up to 40% of FTD patients, with 10% of cases having a clear autosomal dominant inheritance[13,53]. No approved disease-modifying drugs are available for the treatment of FTD and patients are estimated to survive 2-5 years after the clinical diagnosis[13].

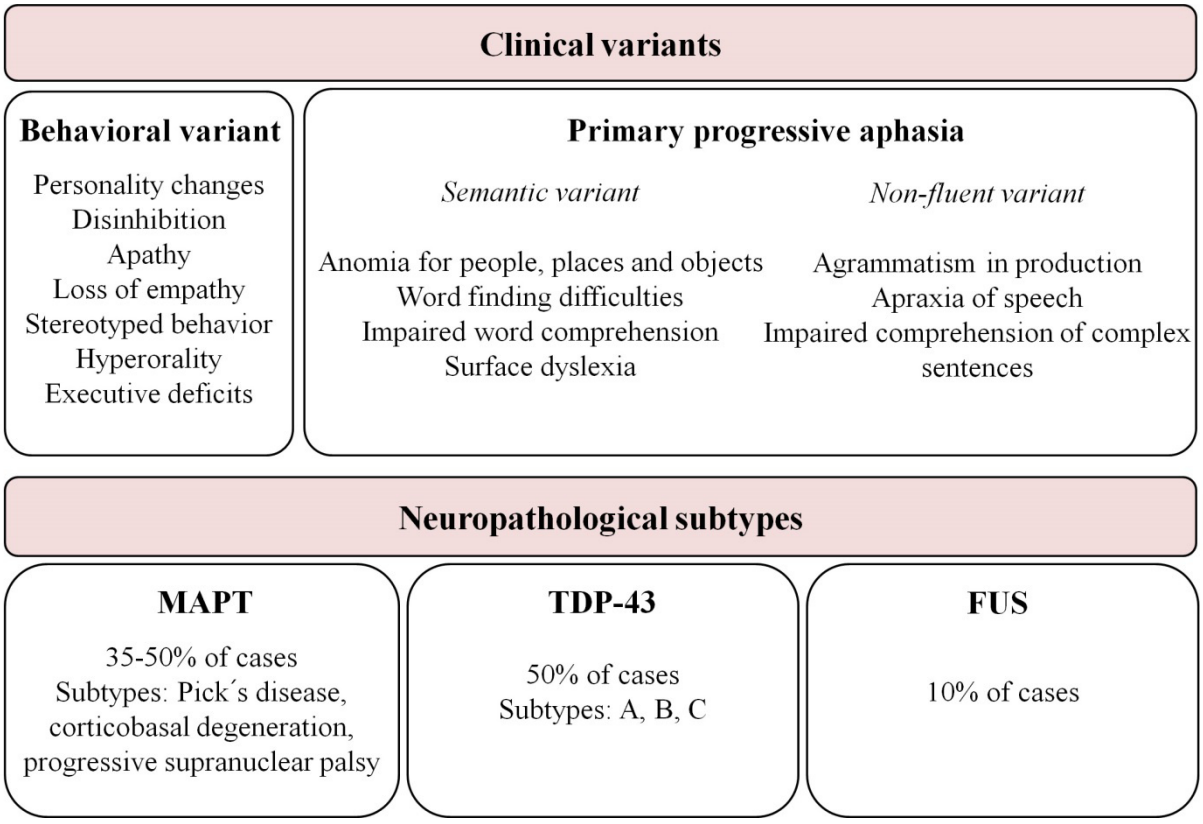

Figure 4 Characteristics of frontotemporal dementia[13]

MAPT, microtubule-associated protein tau; TDP-43, TAR DNA-binding protein with molecular weight 43 kDa; FUS, fused-in-sarcoma

1.2 VASCULAR RISK FACTORS FOR DEMENTIA

It has been well established that traditional vascular risk factors (VRFs), such as hypertension, hypercholesterolaemia, diabetes mellitus, smoking, sedentary behavior and obesity, increase the risk of developing cognitive decline and dementia[54]. These associations are strongest when multiple VRFs are present in mid-life or last from early adulthood and are left untreated[55-58]. The influence of VRFs in late-life on the occurrence of dementia is less certain, as many studies report inverse associations[59-61], probably reflecting that the levels of several VRFs decrease some years before the diagnosis of dementia.

The effect of VRFs on the development of cognitive decline and dementia is mainly explained by the presence of atherosclerosis, arteriolosclerosis and vascular stiffness (Figure 5)[56,62]. The associations between VRFs and dementia are largely mediated by mixed cerebrovascular and neurodegenerative lesions[56,62], which emerge through several mechanisms including insufficient perfusion, hypoxia, inflammation or oxidative stress[56,62]. Each VRF may also uniquely impact the brain. Hypertension may cause cerebral hypoperfusion due to impaired cerebral autoregulation[63]. Diabetes mellitus can lead to neuronal damage as a result of accumulated advanced glycation end-products[64]. Endocrine, inflammatory and thrombotic functions of adipokines may explain the link between obesity and dementia[65].

Furthermore, an established CVD, as a consequence of the exposure to VRFs, may directly contribute to the trajectory towards dementia. Atrial fibrillation, the most common type of arrhythmia, has been found associated with a risk of cognitive impairment and dementia, likely due to embolism, brain hypoperfusion due to irregular heart beat and reduced cardiac output[66]. Some epidemiological studies suggest an association of myocardial infarction with a higher risk of dementia[67,68], however, results are inconsistent[69,70]. The relationship between heart failure and dementia is discussed in the next chapter.

Recent studies, using sensitive MRI techniques, suggest that VRFs may affect the brain already in mid-life. Hypertension was found associated with impairment in white matter integrity, lower cerebral blood flow and cerebrovascular reactivity in individuals at the age of 50[71,72]. In the same cohort, high body mass index and smoking were associated with lower cerebral blood flow. Further, moving against the life course, high systolic blood pressure was found associated with impaired white matter integrity in individuals already at the mean age 39 years[31].

Observational studies implicate a causal relationship between vascular pathology and AD as well as vascular dementia. There is less evidence that cerebrovascular pathology contributes substantially to the occurrence of Lewy body dementias and FTD. Traditional VRFs including blood pressure, diabetes mellitus and cholesterol have not been found associated with a risk of Parkinson´s disease[73]. Interestingly, smoking seems to be a protective factor against Parkinson´s disease[74]. However, concomitant cerebrovascular pathology may modify the course of Parkinson´s disease and contribute to the development of dementia[75-79]. One study indicated that diabetes mellitus may increase the risk of FTD[80], but this finding has not been replicated[81].

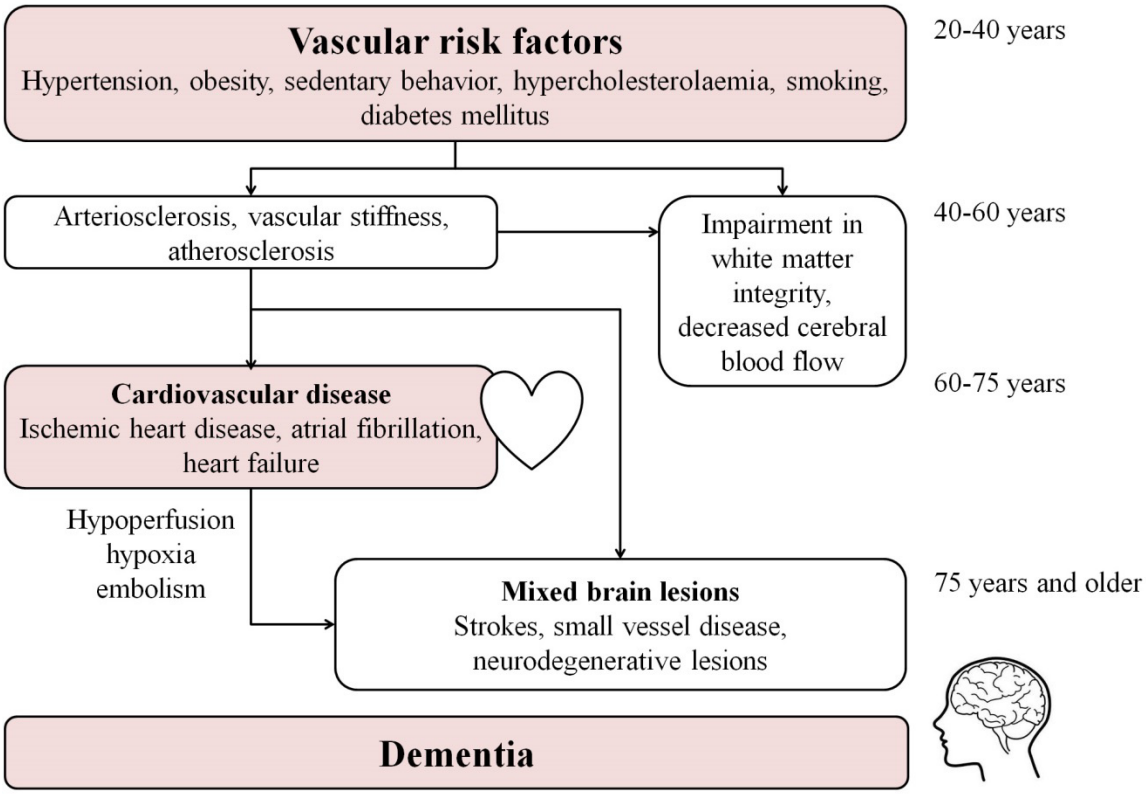

Figure 5 Relationship between vascular risk factors and dementia[82]

1.3 HEART FAILURE

The burden of VRFs and CVD may ultimately lead to heart failure, when the heart is unable to pump blood in order to meet the metabolic needs of the body. Heart failure is a syndrome caused by an abnormality in a structure or a function of the heart, clinically presenting with breathlessness, ankle swelling and fatigue. Its prevalence in the adult population is 2% and is rising to more than 10% among people older than 70 years[83]. In the United States, the burden of heart failure is highest among African Americans who present with symptoms at younger age. One in 100 African Americans develops heart failure before the age of 50, which is 20

times higher than the incidence in Caucasian populations[84]. Approximately half of patients with heart failure have left ventricular ejection fraction below 40% (heart failure with reduced ejection fraction, HFREF), while the rest is affected by heart failure with preserved ejection fraction (HFPEF).

HFREF is characterized by systolic dysfunction that emerges as a consequence of cardiac remodeling following loss of cardiomyocytes, caused by for example myocardial infarction[85]. Activation of the renin-angiotensin-aldosterone system (RAAS) accompanies HFREF and its inhibition is the main treatment strategy for HFREF[83]. Angiotensin-converting enzyme inhibitors (ACEIs) and beta blockers are recommended for all patients with HFREF[83]. In case of intolerance to ACEIs, angiotensin-receptor blockers should be prescribed[83]. In addition, mineralocorticoid receptor antagonists are recommended for patients with left ventricular ejection fraction lower than 35%[83].

On the contrary, HFPEF is driven by aging and comorbidities such as obesity, diabetes mellitus, hypertension and atrial fibrillation[85]. These induce a systemic inflammatory state and microvascular endothelial dysfunction that trigger cardiac remodeling, leading to diastolic dysfunction[85]. No medicines have been shown in clinical trials to improve mortality in patients with HFPEF[83]. The proportion of HFREF among patients with heart failure has been declining and HFPEF, now increasingly recognized as equally serious as HFREF, is projected to become the predominant type in the future[83,86,87].

Despite shared VRFs, it is evident that heart failure may increase the risk of dementia due to insufficient cardiac output, leading to decreased cerebral perfusion (Figure 6)[87]. Moreover, systemic inflammation and endothelial dysfunction driven by comorbidities may put the brain at risk for structural abnormality[87]. Given the expanding proportion of older individuals, it is expected that more people will be affected with both dementia and heart failure in the future. It is unclear how this will affect their prognosis.

Heart failure is preceded by a long pre-clinical period when subtle cardiac dysfunction is frequently present without any clinical symptoms[88]. Markers of subclinical cardiac dysfunction, such as decreased left ventricular ejection fraction, increased left atrial volume or higher left ventricular mass are precursors of incident heart failure[88-91] . These parameters have been found associated with preclinical markers of dementia assessed by MRI, such as loss of brain volume, ischemic lesions and impaired integrity of the white matter[92,93]. Recent studies indicate that antecedents of heart failure occur already in the

young adulthood[94]. From this follows a hypothesis that subclinical cardiac dysfunction may affect aging of the brain as early as in young adulthood.

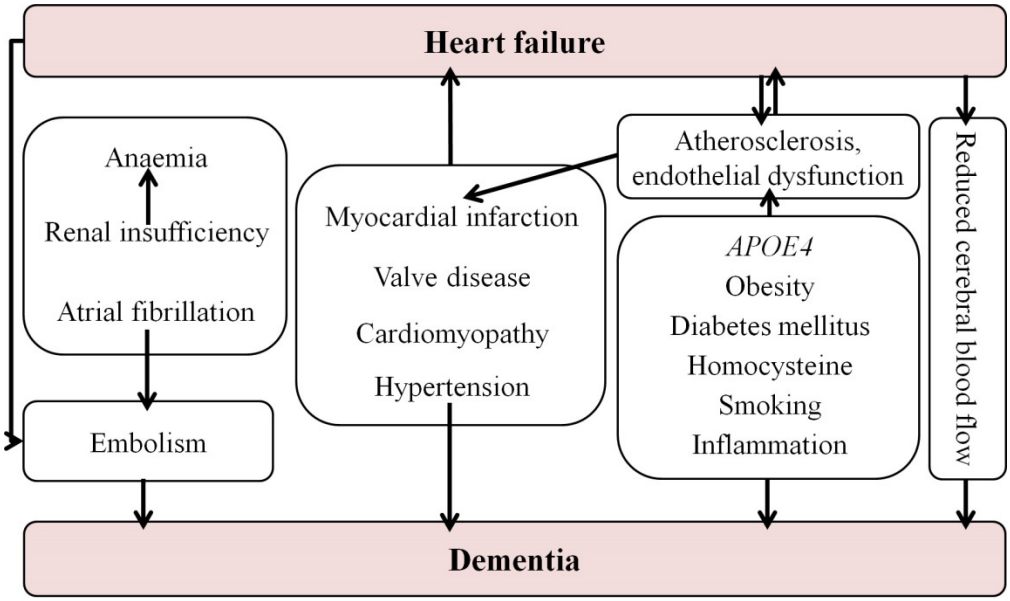

Figure 6 The complex relationship between heart failure and dementia[87]

1.4 CARDIOVASCULAR COMORBIDITIES OF PATIENTS WITH DEMENTIA

When CVDs occur in patients with dementia, they no longer function as risk factors, but accompany dementia as comorbidities and may lead to a greater risk of death and a worse functional status. The prevalence of comorbidities in patients with dementia compared to dementia-free individuals is a matter of debate[95-102]. The often reported lower burden of comorbidities in dementia can be a true finding, may reflect differences in survival (the sicker patients may have died before they developed dementia) or may be due to underdiagnosing of comorbidities. Patients with dementia are not able to sufficiently express discomfort; moreover, physicians may lose sight of other conditions or have low diagnostic ambitions when facing a person with dementia.

There are indications of lower occurrence of myocardial infarction after the diagnosis of dementia[70,103]. Even though underdiagnosing is the most plausible explanation, it cannot be excluded that this is a true finding. Nordström et al. showed that the use of acetylcholinesterase inhibitors, that may have cardioprotective properties, was associated with a lower incidence of myocardial infarction in patients with dementia[103]. Moreover, the levels of VRFs, such as blood pressure, cholesterol and body mass index drop in pre-clinical

stages of dementia[59-61], suggesting that patients with dementia may truly be at a lower risk of acute myocardial infarction.

Conversely, patients with dementia, in particular at more advanced stages, are at a higher risk of developing strokes[104]. Compared to dementia-free individuals, stroke is almost three times more likely to occur in patients with mild dementia and up to seven times more in those with severe dementia[105,106]. This high risk can be explained by cerebrovascular lesions that are already present in patients with dementia and are associated with a higher risk of subsequent strokes[106-108]. Moreover, antipsychotic drugs, used to treat behavioral symptoms in dementia, may cause strokes as well[109].

Several studies suggested a lower occurrence of diabetes mellitus, cerebrovascular disease and ischemic heart disease in patients with Parkinson´s disease[75,110,111]. This may be explained by a lower severity of atherosclerosis due to non-smoking as well as the failure of the sympathetic nervous system, which possibly plays a role in the genesis of CVD[110]. However, conflicting evidence exists[76] as well as indications of a higher occurrence of heart failure in Parkinson´s disease[75], likely caused by medication[112]. Data on comorbid CVD in patients with diagnosed Lewy body dementias and FTD are scarce, due to a lack of large patient cohorts.

1.5 TREATMENT OF CARDIOVASCULAR DISEASES IN PATIENTS WITH DEMENTIA

Patients with dementia are treated less intensively for CVDs, including ischemic heart disease, cerebrovascular disease, atrial fibrillation and heart failure[113-117]. The potential under-treatment of CVDs occurs most often in patients with severe dementia and among those living in nursing homes[118]. Whether this lower intensity can be considered as under-treatment requires more knowledge about what is the appropriate management of CVDs in patients with dementia. Ideally, the adequate management of CVDs in dementia should slow down the progression of cognitive and functional decline and reduce the risk of death. Conversely, under- or overtreatment may do the opposite. There are no specific guidelines for treating CVDs in patients with dementia, likely because of lacking evidence due to their exclusion from clinical trials[119,120].

The reasons for potential under-treatment of CVDs in dementia may be multiple (Figure 7). Patients with dementia are more likely to be physically frail, face more severe adverse effects from drug interactions and are at a higher risk of death[121-123]. Moreover, they often suffer

from orthostatic hypotension, in particular those with Lewy body dementias, which complicates the management of CVDs[124-126]. Patients with advanced cognitive impairment and those who live alone have problems with administration and adherence to drug regimens[127,128]. We can deduce that the results from clinical studies may not be simply conveyed and generalized to patients with dementia, who probably constitute a special patient population[123].

Several other factors may hinder receiving the optimal treatment for CVD. Patients with dementia may have worse access to health care, due to their dependency on caregivers and cognitive impairment. Moreover, dementia can be perceived as a stigma[129] and together with lower socioeconomic status, associated with dementia[130], may influence the attitude of physicians when deciding about the treatment.

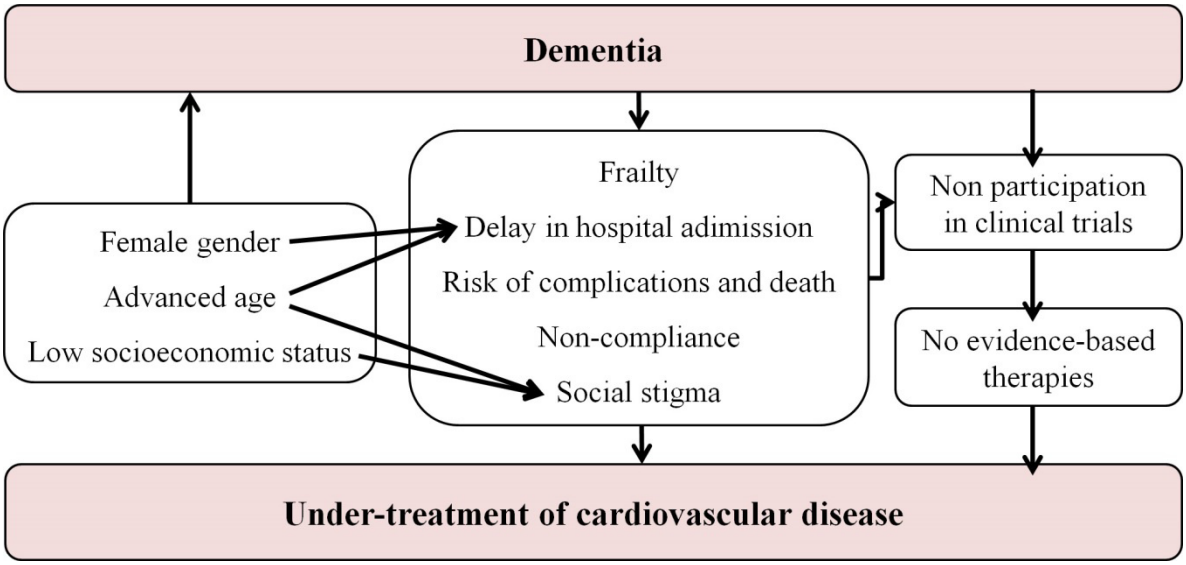

Figure 7 Suggestions of mechanisms leading to less optimal treatment of CVD in patients with dementia

1.6 MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH DEMENTIA

Acute myocardial infarction is characterized by irreversible cell death in myocardium due to insufficient blood supply. According to echocardiographic findings, it presents as myocardial infarction with ST-elevation (STEMI), or myocardial infarction without ST-elevation (NSTEMI)[131,132]. NSTEMI accounts for 75% of cases of acute myocardial infarction in octogenarians[133,134]. The incidence of acute myocardial infarction, in particular of STEMI, has been declining[135].

Mortality rates from acute myocardial infarction have significantly dropped over the past decades, largely due to the use of invasive procedures such as coronary angiography and revascularization with percutaneous coronary intervention (PCI)[135]. An early invasive strategy for STEMI patients and assessment for the invasive management in patients with NSTEMI are recommended[131,132]. This has been successfully implemented, especially in younger individuals and men[131-133].

Several reasons hinder the use of invasive procedures in the treatment of acute myocardial infarction in older patients. The most typical symptom, chest pain, is reported only in 40% of octogenarians[132], who usually experience atypical symptoms, such as dyspnea, nausea or syncope[131]. Moreover, prompt arrival to the hospital is necessary to perform revascularization, and older individuals, especially women, frequently have pre-hospital delays[131].

Dementia is associated with a higher mortality from acute myocardial infarction and is also a barrier for receiving coronary angiography and PCI[113,136-138]. As the benefits of the invasive management are highly uncertain in patients with dementia, clinicians face difficult decisions[113,136-138]. One study, however, found that the use of PCI in patients with dementia was associated with lower in-hospital mortality[136], indicating that individuals with dementia may in fact benefit from it.

2 AIMS

The objective of this thesis is to characterize the burden of CVD in patients with dementia, their treatment and impact on survival, with an emphasis on heart failure and acute myocardial infarction. Further aim is to study whether cardiac parameters in young adulthood may influence brain structure in mid-life.

Specifically, we aimed to study

- factors associated with prescription of cardiovascular drugs in patients with dementia (Paper I)
- clinical characteristics of patients with heart failure and dementia and their mortality (Paper II)
- frequency of chronic CVDs in patients with dementia and their association with mortality (Paper III)
- proportion of patients with dementia who were managed invasively for acute myocardial infarction; and whether this was associated with longer survival (Paper IV)
- associations of echocardiograhic parameters in young adulthood with brain MRI markers in mid-life (Paper V)

3 METHODS

We performed 5 observational cohort studies. Papers I-IV are based on patients registered in the Swedish Dementia Registry (SveDem). Their information has been linked with data from the Swedish Heart Failure Registry (RiksSvikt), the Swedish Patient Register, the Swedish Prescribed Drug Register and the Swedish Population Register. Paper V is based on data from an American population-based study Coronary Artery Risk Development in Young Adults (CARDIA).

3.1 DATA

SveDem is a Swedish national registry that aims to monitor and ensure the quality of the diagnostic work-up, treatment and care of patients with dementia in Sweden and was previously described in detail[139]. Briefly, it was established in 2007 with the aim to register all individuals at the time of dementia diagnosis and follow them yearly. In 2013, it included 36 383 registrations of patients who were newly diagnosed by physicians in memory clinics (65% of patients) or primary care (35% of patients). Patients are diagnosed with one of 8 dementia disorders (Figure 8). Information about age, gender, living conditions, results from the Mini Mental State Examination (MMSE), diagnostic procedures and treatment is recorded.

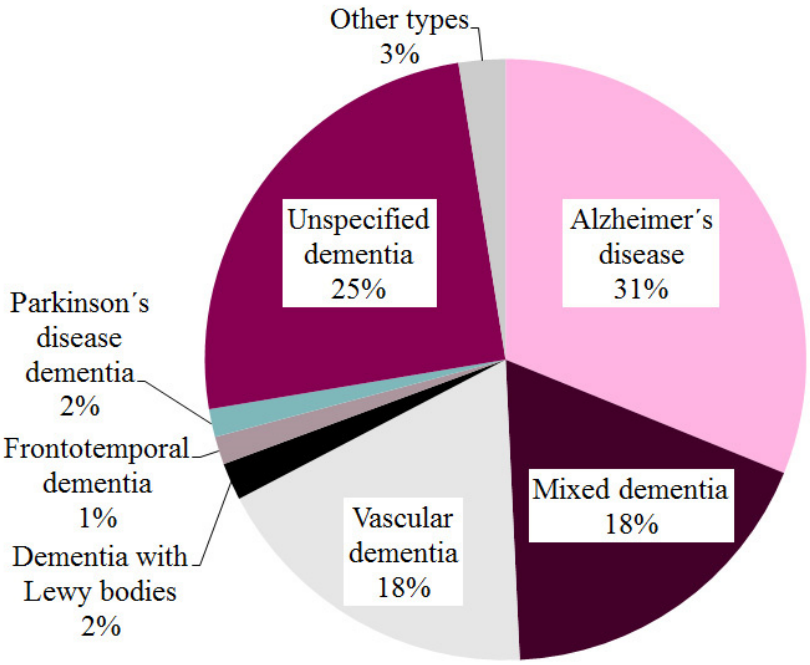

Figure 8 Distribution of dementia disorders in SveDem

RiksSvikt is a Swedish national register that was established in 2003 with the goal to monitor and improve the care of patients with heart failure in Sweden[140]. In 2013, it included 55 313 patients who were registered in a hospital (93% of patients) or in primary care (7% of patients). Information about demographic data, medication, duration, type and severity of heart failure is registered.

The Swedish Patient Register covers in-patient and out-patient care encounters in Sweden[141]. One main diagnosis and up to 21 additional diagnoses are registered with an International Classification of Diseases (ICD) code together with demographics, administrative information and surgical procedures. The Swedish Prescribed Drug Register contains information on all dispensed prescriptions at Swedish pharmacies to the entire Swedish population[142]. Drugs are coded according to the Anatomical Therapeutic Chemical Classification system.

CARDIA was established in 1985 in 4 centers in the United States (Birmingham, Chicago, Minneapolis and Oakland) with the aim to examine the trajectories of CVD starting in young adulthood[143]. The original cohort consisted of 5 115 persons (age 18-30 years, 52% African Americans, 55% women). At the 5th follow-up year, the study participants received an ultrasound examination of the heart[144]. In 2010, 72% of the surviving cohort underwent the 25th follow-up exam. From those, 719 persons participated in the brain MRI examination (CARDIA Brain MRI Sub-study)[72].

3.2 DEFINITIONS

In Papers I-IV, dementia was diagnosed according to ICD 10[145]. In addition, McKeith criteria were used for DLB[146], Lund-Manchester criteria for FTD[147] and Movement Disorder Society Task Force criteria for PDD[46]. Unspecified dementia is registered if the dementia etiology is unknown or if the diagnostic tests have not been performed. Other dementia types include less frequent dementia disorders, such as alcohol-related dementia.

In Paper I, we studied prescription of cardiovascular drugs in patients registered in SveDem. These include antihypertensive drugs, anticoagulants, lipid-lowering drugs, anti-diabetics and anti-angina medication. The information is based on medical records, thus was obtained during medical examination, directly from patients or indirectly from caregivers.

In Paper II, we studied patients with heart failure and dementia, registered in SveDem and RiksSvikt. We divided patients into 3 groups according to type of heart failure: HFPEF (ejection fraction ≥ 40%), HFREF (ejection fraction < 40%) and heart failure with missing ejection fraction, when the value of ejection fraction was absent in RiksSvikt. Further, we divided patients into 4 groups based on type of dementia disorder: AD, mixed dementia, vascular dementia and other dementia disorders.

In Paper III, we characterized chronic CVDs based on records in the Swedish National Patient Register from 2000 until 2012. Following ICD codes were used: ischemic heart disease (I20-I25), atrial fibrillation and flutter (I48), heart failure (I50), cerebrovascular diseases (I60-I69) and diabetes mellitus (E10-E13).

In Paper IV, we identified patients who suffered an acute myocardial infarction after the diagnosis of dementia by the following codes in the Swedish National Patient Register: STEMI (I21.0-I21.3), NSTEMI (I21.4) and unspecified acute myocardial infarction (I21.9). Invasive management was defined as coronary angiography (AF037) and percutaneous coronary intervention (FNG02 or FNG05), occurring during the same hospitalization. Comorbidity was defined by a sum of 9 diseases (shock, diabetes mellitus, heart failure, cancer, cerebrovascular disease, pulmonary edema, acute renal disease, chronic renal disease, cardiac dysrhythmia)[148] or total number of drugs[149].

In Paper V, cardiac parameters were obtained by a two-dimensional and guided M-mode echocardiography[144]. Parameters of interest were left ventricular ejection fraction, left atrial volume and left ventricular mass. Markers of brain health obtained by MRI were white matter fractional anisotropy (a measure of white matter integrity estimated from DTI), volumes of normal brain tissue (total brain, gray matter and white matter) and volume of abnormal white matter, including tissue damaged due to ischemia, demyelination and inflammation. The volume of abnormal white matter was classified as none (0 cm^3), little (≤ 0.3 cm^3) and high (> 0.3 cm^3).

3.3 STATISTICAL ANALYSIS

The selection of study samples is presented on Figure 9. Briefly, for Paper I we selected 19 743 patients registered in SveDem between 2007 and 2012, who had information on the use of cardiovascular medication. Paper II included patients registered in SveDem and RiksSvikt (n=775). Patients registered in SveDem between 2007 and 2012 were the basis for

Paper III (n=29 630) and those who suffered acute myocardial infarction after the dementia diagnosis were included in Paper IV (n=525). Participants in CARDIA with data on brain MRI and echocardiography were selected for Paper V (n=648).

All analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp. Armonk, NY). Descriptive data is presented as mean ± standard deviation (SD), median (25%; 75%) / interquartile range and frequency (%). To compare characteristics between groups, we used an independent sample t-test / 1-way analysis of variance for continuous variables with normal distribution, Mann-Whitney U test / Kruskal-Wallis test for continuous variables with skewed distribution and chi-squared test / Fisher exact test for categorical variables.

In Paper I, we used binary logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for associations of patients´ characteristics (age, gender, MMSE, living conditions, dementia disorder) with the use of cardiovascular drugs.

In Paper II, we used multinomial logistic regression to explore associations between type of dementia disorders and type of heart failure. We analyzed survival with Kaplan-Meier curves and used log rank tests to compare groups. We followed the patients from the date they were registered in both SveDem and RiksSvikt until the death or the end of follow-up in October 2013.

In Paper III, we performed multinomial logistic regression to estimate OR with 95% CI for associations of CVD with dementia disorders, when compared to AD. To study mortality associated with CVD, we applied Cox regression to estimate hazard ratio (HR) with 95% CI for associations of CVD with all-cause mortality. The patients were followed up from the time of dementia diagnosis until their death or the end of the follow-up in October 2013.

In Paper IV, we applied binary logistic regression to examine the associations of patients´ characteristics with the invasive management of myocardial infarction. We assessed survival by Kaplan-Meier curves and then used Cox regression to estimate HR with 95% CI for an association of the use of the invasive procedures with all-cause mortality. The patients were followed-up from the date of myocardial infarction until their death or to December 2012.

In Paper V, we applied linear regression to investigate associations of cardiac parameters with white matter fractional anisotropy, volume of total brain, gray matter and white matter. We used logistic regression to assess the associations of the cardiac parameters with abnormal white matter volume.

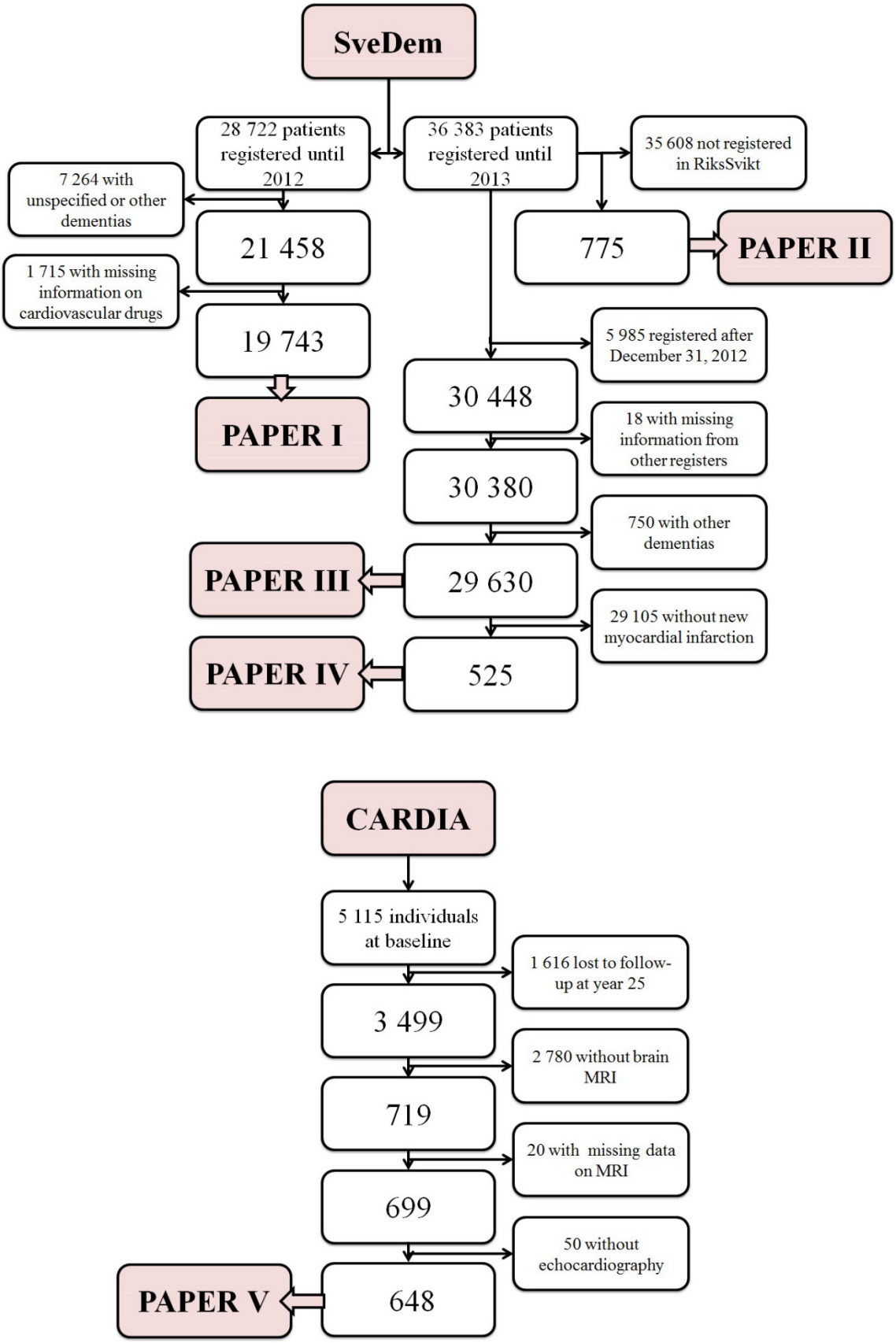

Figure 9 Selection of the study samples

4 ETHICAL CONSIDERATIONS

Research ethics deals with the concepts of autonomy and personal integrity of the studied individuals. Autonomy relates to the right of everyone to make their own decisions. Personal integrity comprises privacy, dignity and presupposes respect for other people´s feelings and their "right to be forgotten". Data concerning health is considered sensitive, is protected by secrecy and requires ethical vetting. In order to maintain people´s autonomy and personal integrity while performing research, an informed consent is usually required.

Papers I-IV were approved by the regional ethical review board in Stockholm. No written informed consent was acquired. Patients and their relatives were informed about registrations into SveDem and RiksSvikt and had a right to decline participation and have their information removed. It needs to be acknowledged that patients with dementia have limited ability to decide on their own whether they want to be registered in SveDem due to their low cognitive functions. However, according to the principle of justice and equality, everybody should be provided appropriate access to participation in research, including underrepresented groups and individuals who cannot consent themselves[150-152].

Unlike quality registers, there is no possibility to have data removed from Swedish health registers (the Swedish Patient Register and Swedish Prescribed Drug Register). The advantage of using data from registers is that this is a timely and cost-effective way that does not include risks by interventions. To reduce the potential harm of utilizing sensitive personal information, data were de-identified and results are presented only on a group level.

For Paper V, all participants in CARDIA provided a written informed consent at each exam and institutional review boards from each center annually approve the study. A separate approval was given by the institutional review boards of the participating sites and the institutional review board covering Intramural Research at the National Institute of Aging. Another written consent for the CARDIA MRI Sub-study was obtained.

5 RESULTS AND DISCUSSION

5.1 CARDIOVASCULAR MEDICATION IN PATIENTS WITH DEMENTIA (PAPER I)

From 19 743 patients with dementia (58% women, mean age 79 years), 70% (n=13 847) were prescribed cardiovascular drugs. Their use was highest in patients with vascular dementia (84%) and lowest in frontotemporal dementia (53%, Figure 10). Patients who were prescribed cardiovascular drugs were older (80 vs. 77 years; p<0.001), less frequently women (56% vs. 64%; p<0.001), had a slightly higher MMSE score (21.4 vs. 21.3; p<0.001) and lived less frequently alone (44% vs. 46%; p=0.01).

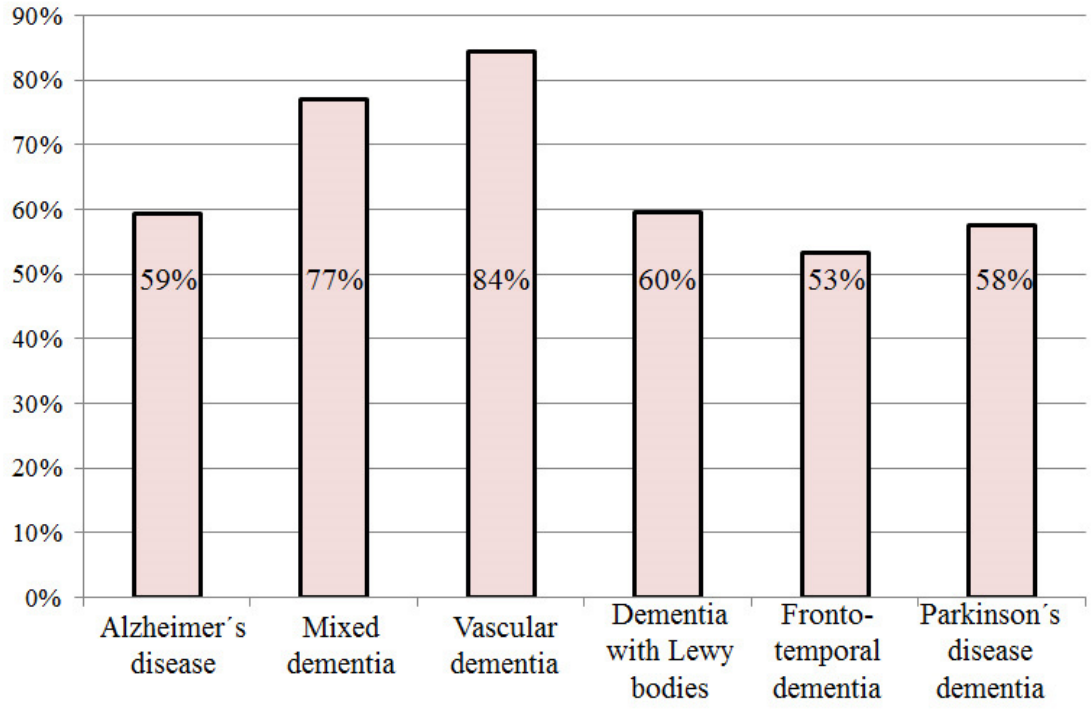

Figure 10 Use of cardiovascular drugs in different dementia disorders

In multivariate analysis (Table 2), we found that higher age (OR 1.02; 95 CI 1.01-1.02), male gender (OR 1.45; 95% CI 1.34-1.57) and a higher MMSE score (OR 1.02; 95% CI 1.01-1.03) were associated with the use of cardiovascular drugs. On the other hand, living alone was inversely associated with cardiovascular drugs (OR 0.75; 955 CI 0.69-0.81). When compared to AD, patients with mixed dementia and vascular dementia had higher odds of taking cardiovascular drugs, while the opposite was found for DLB (OR 0.71; 95% CI 0.58-0.87) and PDD patients (OR 0.31; 95% CI 0.24-0.40).

Table 2 Associations of patients´ characteristics with the use of cardiovascular drugs

	OR (95% CI)
Age	1.02 (1.01-1.02)**
Male gender	1.45 (1.34-1.57)**
MMSE	1.02 (1.01-1.03)**
Living alone	0.75 (0.69-0.81)**
Dementia disorders	
Alzheimer´s disease	Reference
Mixed dementia	1.57 (1.43-1.73)**
Vascular dementia	2.14 (1.89-2.44)**
Dementia with Lewy bodies	0.71 (0.58-0.87)**
Frontotemporal dementia	0.91 (0.71-1.17)
Parkinson´s disease dementia	0.31 (0.24-0.40)**

MMSE, Mini Mental State Examination; OR, odds ratio; CI, confidence interval
*** p<0.001*
ORs with 95% CI are derived from binary logistic regression and are estimates for associations of clinical characteristics with the use of cardiovascular drugs. All variables in this table as well as use of cholinesterase inhibitors, memantine and total number of drugs are included in the model.

In Paper I, we studied the use of cardiovascular drugs in SveDem, a Swedish quality register of patients with dementia. This information may be viewed as a proxy for cardiovascular comorbidity or indicate clinical practice of treating CVD. The frequency of cardiovascular drugs among patients with dementia (70%) is slightly higher than in the general population of older Swedes (mean age 82 years), from whom 66% use cardiovascular drugs[153], but lower than in other dementia cohorts[154,155].

In Spain, almost 80% of patients with dementia registered in specialist clinics receive cardiovascular drugs, despite having a lower prevalence of CVD compared to Sweden[154]. In Germany, 90% of individuals with dementia are prescribed at least one cardiovascular drug[*]. In Finland, 80% of AD patients are treated with cardiovascular medication[155]. These differences may indicate less aggressive treatment of CVD in patients with dementia in Sweden when compared to other countries.

Three main limitations of this study possibly lead to underestimation of the use of cardiovascular drugs in AD. First, no guidelines clearly specify how to deal with cerebrovascular pathology that is present in around 50% of AD patients[5], causing

[*] Personal communication; the information concerns drugs prescribed by general practitioners and is based on Disease Analyzer database

inconsistency in the amount of cerebrovascular disease allowed for the diagnosis of AD vs. mixed dementia[8,156]. Second, we excluded patients with unspecified dementia, who have a high cardiovascular comorbidity burden, and likely include a high proportion of patients with AD. These patients, predominantly registered to SveDem in primary care, may have not received a specific dementia diagnosis due to their high age, frailty and thus perceived marginal benefits from an extended diagnostic work-up. Third, this study is limited by circular reasoning, as patients with more CVD and thus more cardiovascular drugs are more likely to be diagnosed with vascular dementia.

The associations of higher age and male gender with the use of cardiovascular drugs confirm that the occurrence of CVD increases with age and men are burdened by more CVD compared to women. The possibility that men receive more treatment for CVD than women cannot be excluded. However, the gender disparity exists in particular in acute cardiac care, to which women may have a lower access than men[157,158]. On the other hand, women have more contact with non-acute care and are prescribed more drugs[159].

The association of slightly higher cognitive status with the use of cardiovascular drugs is modest, but may indicate that physicians withdraw medication in patients with more advanced cognitive impairment. Patients with cardiovascular drugs are less likely to live alone, probably because solitary living patients do not seek medical care and/or have difficulties with adherence to drugs[160]. An alternative explanation is that people who are healthier are able to live alone for a longer time, while those with more cardiovascular comorbidity may move in with relatives or to a nursing home.

Patients with PDD and DLB were the least likely to receive cardiovascular drugs, which suggests a lower prevalence or less intensive treatment of CVD. The following supports lower prevalence of CVD in Lewy body dementias: First, while CVDs are the most common causes of death in the general population in Sweden as well as in the whole SveDem cohort, patients with Lewy body dementias are at the highest risk of dying from respiratory diseases[161]. Second, several studies report a lower burden of CVD in patients with Parkinson´s disease[75,110,111]. On the other hand, autonomic dysfunction, which is highly frequent in patients with Lewy body dementias, complicates the management of CVD, mainly hypertension, which may lead to withdrawal of cardiovascular medication[124]. To conclude, both the possibility of a lower prevalence of CVD and its less frequent treatment, likely explain it.

5.2 CHARACTERISTICS OF PATIENTS WITH HEART FAILURE AND DEMENTIA (PAPER II)

A total number of 775 patients with heart failure and dementia were studied (mean age 82 years, 55% of men; Table 3). The most common type of heart failure was HFPEF (38%). 34% of patients had HFREF and 28% had missing information on ejection fraction. The most frequent dementia disorder was vascular dementia (36%), 28% of patients had other dementias, 20% mixed dementia and 16% AD. Other dementias included 186 cases diagnosed with unspecified dementia, 8 DLB, 6 FTD, 6 PDD and 15 with other types of dementia. There were no significant associations between dementia disorders and types of heart failure.

The patients were followed for an average of 1.5 years, there were 264 deaths per 1000 person-years. For the whole population, one-year survival rate was 76%. Individuals with missing information on ejection fraction had the lowest one-year survival rate (72% vs. 79% in HFPEF vs. 76% in HFREF), but there was no statistically significant difference (p=0.2 from log-rank test). AD patients had the highest one-year survival rate (80% vs. 74% in mixed dementia vs. 75% in vascular dementia vs. 77% in other dementias), without statistical significance (p=0.5 from log-rank test).

Table 3 Characteristics of patients with dementia and heart failure (n=775)

Characteristic	Value
Registration to RiksSvikt in inpatient sector, n (%)	509 (65.7)
Registration to SveDem in specialist center, n (%)	493 (63.6)
Systolic blood pressure, mean ± SD	130.6 ± 20.6
Heart rate, mean ± SD	74.8 ± 15.6
MMSE, mean ± SD	21.1 ± 4.9
Comorbidity, n (%)	
Ischemic heart disease	402 (51.9)
Atrial fibrillation	457 (59.0)
Diabetes mellitus	177 (22.8)
Drugs, n (%)	
RAS antagonists	570 (73.5)
Beta blockers	624 (80.5)
Diuretics	614 (79.2)
Anticoagulants	280 (36.1)
Acetylcholinesterase inhibitors	198 (25.5)
Memantine	66 (8.5)
Total number of drugs	8.1 ± 3.2

MMSE, Mini Mental State Exam; RAS, renin-angiotensin system; SD, standard deviation

Paper II suggests that patients with heart failure and dementia constitute an old and rather underdiagnosed population. The number of individuals found in both SveDem and RiksSvikt was low, which may be explained by the incomplete coverage of the quality registers, but also likely reflects down-prioritization of these patients in the health care system. A large proportion of patients had missing information on the level of ejection fraction, suggesting low diagnostic and probably therapeutic ambitions of physicians. Similarly, patients with unspecified dementia were highly represented, possibly due to marginal benefits expected from advanced diagnostic work-up.

There were no associations between types of heart failure and dementia disorders and this study cannot support the role of a type of heart failure in the genesis of a specific dementia disorder. The most common type of heart failure was HFPEF, a syndrome that is projected to be the leading type of heart failure in future. Given its similarities with AD, such as strong correlation with age, female gender, inflammation and exposure to VRFs, HFPEF is expected to largely co-exist with AD[85,87]. We observed a trend that vascular dementia was slightly more common in HFREF, while AD accounted for a smaller proportion in this subgroup, indicating a stronger role of vascular disease in the occurrence of HFREF.

One year survival rate of the patients was lower than in the general population of Swedish patients with heart failure (80%)[162], possibly suggesting that dementia may contribute to worse prognosis of patients with heart failure. Missing information on ejection fraction may reflect low diagnostic ambitions, perhaps due to age, frailty and/or comorbidities, and has therefore been suggested as a marker of adverse outcomes[163]. Our study cannot support this, however, we observed a trend towards a higher risk of death in patients who had missing data on ejection fraction. The lack of significant associations may also be caused by a low sample size.

5.3 CARDIOVASCULAR COMORBIDITIES OF PATIENTS WITH DEMENTIA (PAPER III)

In a cohort of 29 630 patients with dementia (mean age 79 years, 59% women), the most common CVD was ischemic heart disease (23%), followed by cerebrovascular diseases (20%) and atrial fibrillation (19%; Figure 11). The proportion of all CVDs was highest in patients with vascular dementia. The frequency of ischemic heart disease, atrial fibrillation and heart failure was lowest in FTD. Cerebrovascular diseases occurred least in AD and diabetes mellitus had the lowest frequency in PDD and DLB.

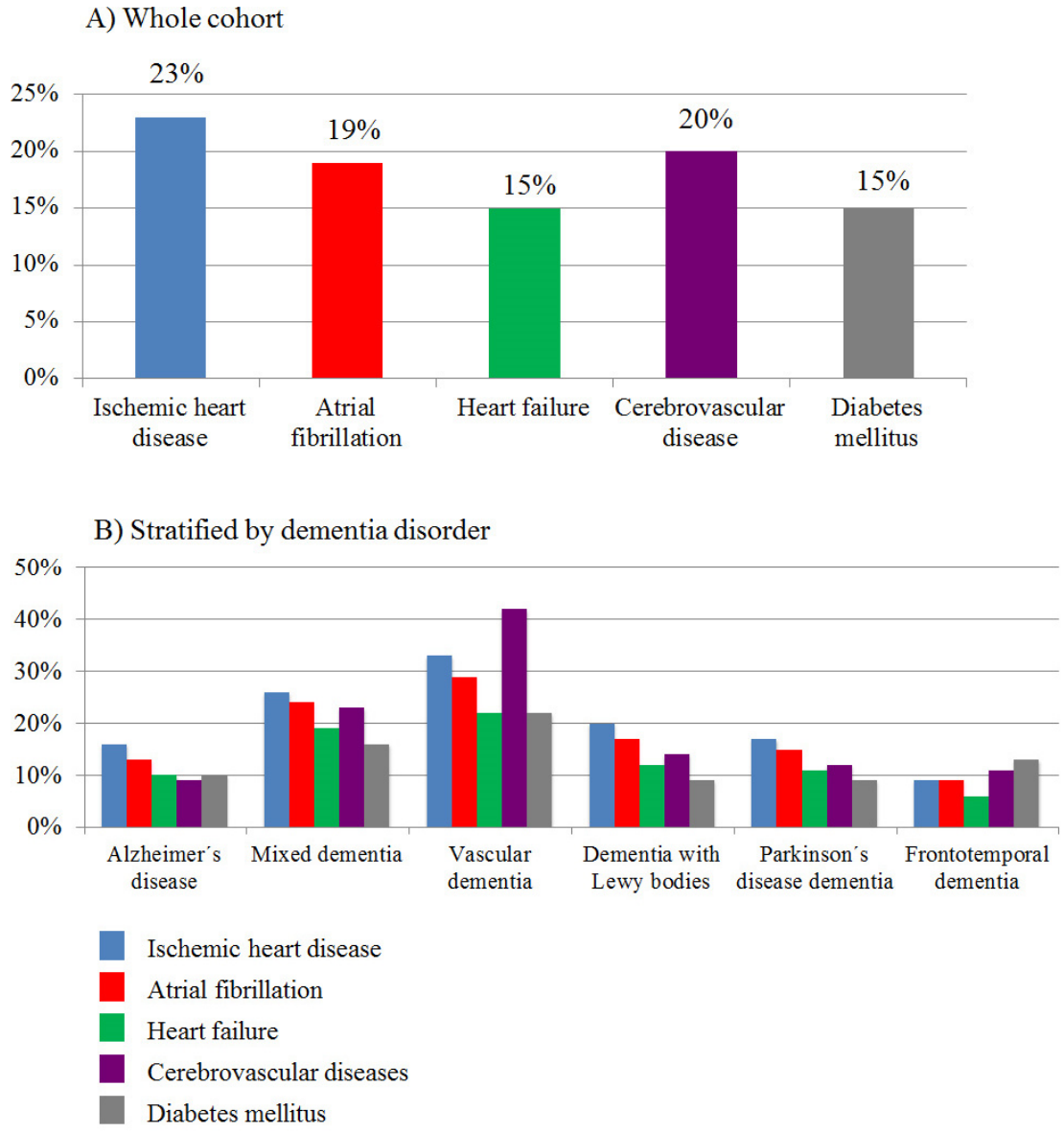

Figure 11 Frequency of cardiovascular disease in patients with dementia

In adjusted analysis (Figure 12), when compared to AD, diabetes mellitus was inversely associated with PDD (OR 0.40; 95% CI 0.27-0.59) and DLB (OR 0.59; 95% CI 0.44-0.80). Further, ischemic heart disease was negatively associated with PDD (OR 0.73; 95% CI 0.55-

0.98) and FTD (OR 0.66; 95% CI 0.45-0.95). On the other hand, cerebrovascular disease was more likely to occur in DLB (OR 1.43; 95% CI 1.12-1.83).

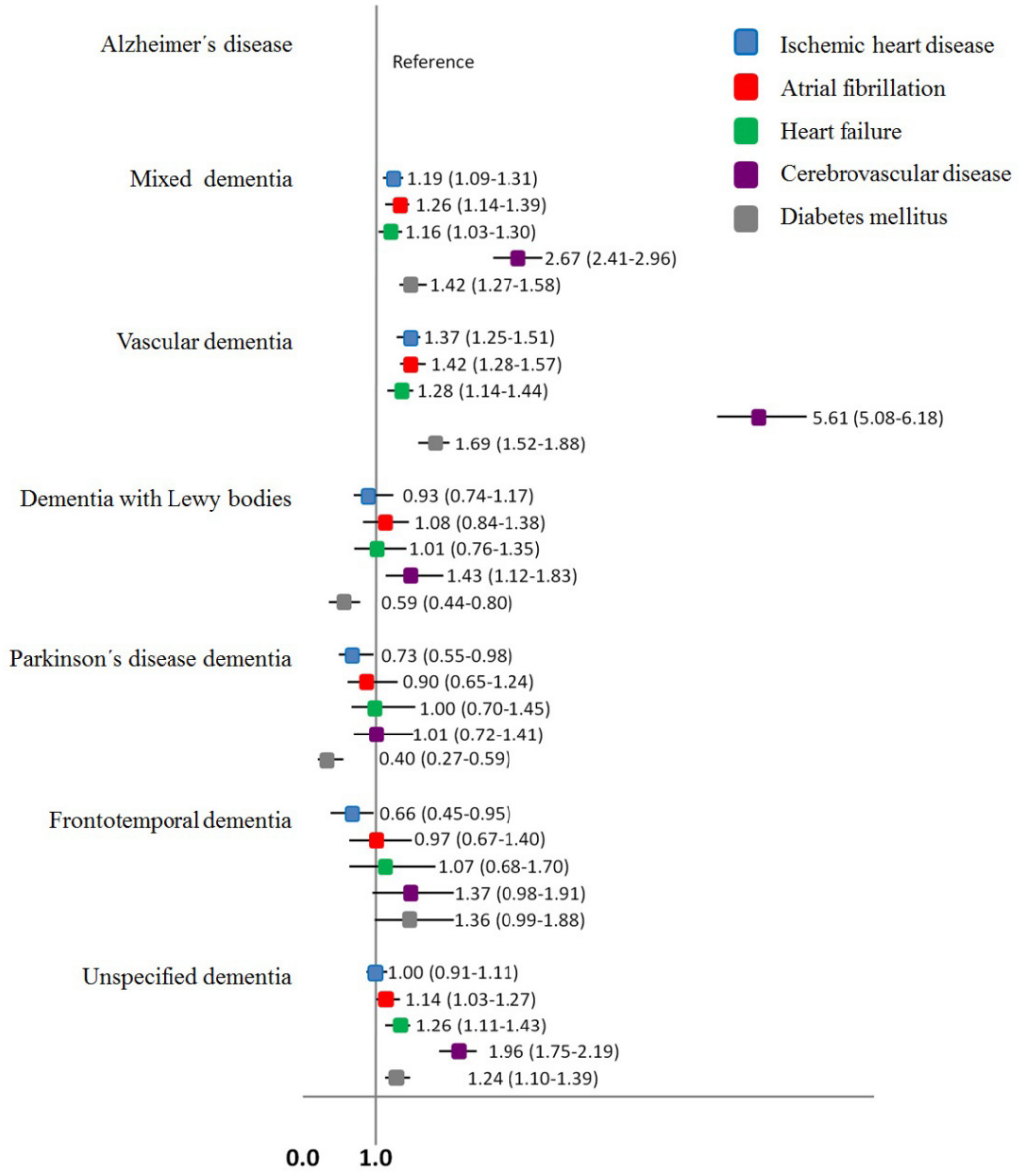

Figure 12 Associations of cardiovascular diseases with dementia disorders, adapted from[164]

Results are derived from multinomial logistic regression and presented as OR with 95% CI for associations of a cardiovascular disease with dementia disorders (with Alzheimer´s disease as a reference), adjusted for age, gender, MMSE, living conditions, registration unit, total number of drugs and other cardiovascular diseases.
OR, odds ratio; CI, confidence interval; MMSE, Mini Mental State Examination

During the median follow-up of 847 days, 27% of patients died. In the whole cohort, all CVDs were associated with an increased risk of death. Heart failure was the strongest predictor of mortality (HR 1.54; 95% CI 1.44-1.65; Table 4).

Table 4 Associations of cardiovascular diseases with risk of death

	HR (95% CI)	
	Model 1	Model 2
Ischemic heart disease	1.41 (1.34-1.48)*	1.28 (1.20-1.36)*
Atrial fibrillation	1.69 (1.60-1.78)*	1.35 (1.27-1.44)*
Heart failure	1.98 (1.87-2.09)*	1.54 (1.44-1.65)*
Cerebrovascular diseases	1.40 (1.33-1.48)*	1.33 (1.25-1.41)*
Diabetes mellitus	1.35 (1.27-1.44)*	1.45 (1.29-1.62)*

** p<0.05*
Results are derived from Cox regression and are presented as HR with 95% CI for associations of cardiovascular diseases with all-cause mortality. Model 1is adjusted for age, gender, MMSE and type of dementia disorder. Model 2 adjusted also for living condition, registration unit, total number of drugs, other cardiovascular diseases and cardiovascular drugs.
HR, hazard ratio; CI, confidence interval; MMSE, Mini Mental State Examination

When stratified by dementia disorder (Figure 13), all CVDs were associated with a higher risk of death in AD, mixed dementia and vascular dementia. In DLB patients, only ischemic heart disease was associated with an increased risk of death (HR 1.72; 95% CI 1.16-2.55). In PDD patients, heart failure and diabetes mellitus were linked to a higher mortality risk (HR 3.06; 95% CI 1.74-5.41 and HR 3.44; 95% CI 1.31-9.03, respectively). Ischemic heart disease and atrial fibrillation were predictors of death in FTD patients (HR 2.11; 95% CI 1.08-4.14 and HR 3.15; 95% CI 1.60-6.22, respectively).

In Paper III, we investigated the burden of 5 chronic CVDs in patients with dementia and their association with mortality. Being derived from a hospital-discharge register, that does not reflect the true prevalence rates; the information on CVDs may be underestimated. The frequency of all CVDs in our cohort is higher when compared to 70-80 years old individuals from a Swedish population-based study[165-169], supporting the role of CVD in the genesis of dementia. Following prevalence of CVD is reported: 8-9% for diabetes mellitus, 15-16% for ischemic heart disease or cerebrovascular disease, 10% for atrial fibrillation and 10% for heart failure[165-169].

All CVDs were predictors of death in the whole cohort, in accord with evidence that CVDs are the commonest causes of death in the general population as well as in patients with dementia[161]. Heart failure was the strongest predictor of death, which is in agreement with reports of its unfavorable prognosis in the elderly[86,170]. After stratification by dementia disorders, all CVDs were predictors of death in patients with AD, mixed and vascular dementia, while we observed different patterns in other dementia disorders.

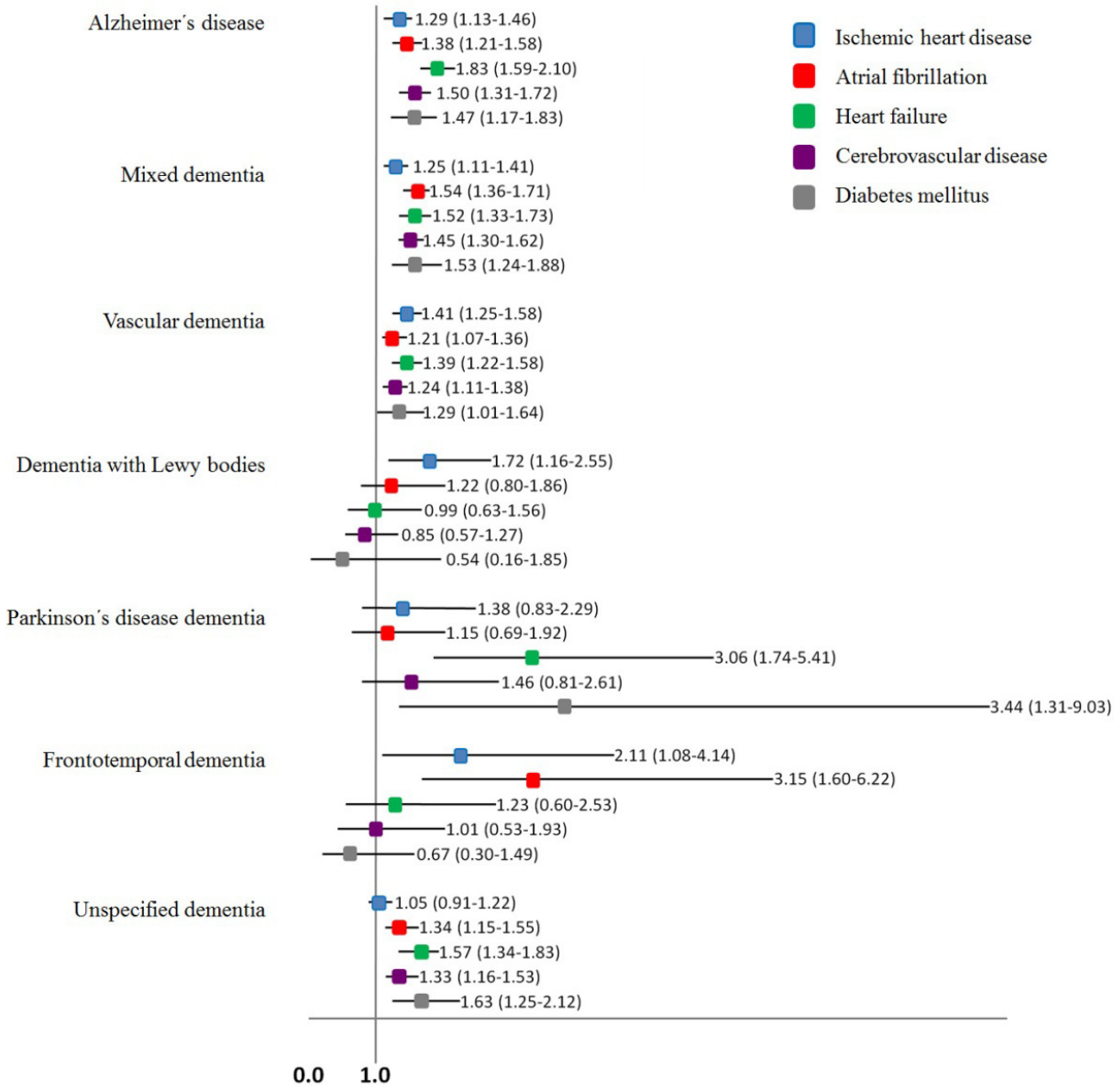

Figure 13 Associations of cardiovascular diseases with risk of death, adapted from[164]

Values are derived from Cox regression and are presented as HR with 95% CI for associations of cardiovascular diseases with all-cause mortality, adjusted for age, gender, MMSE, living condition, registration unit, total number of drugs, other cardiovascular diseases and cardiovascular drugs.
HR, hazard ratio; CI, confidence interval; MMSE, Mini Mental State Examination

Contributing to the evidence of a lower burden of CVD in Lewy body dementias[110,171], we found a lower occurrence of diabetes mellitus in patients with DLB and PDD. A previous study on SveDem data showed that body mass index, a major risk factor for diabetes mellitus, was lowest among patients with DLB and PDD[172]. Despite its lower frequency, diabetes mellitus was a strong predictor of mortality in PDD patients. Previous studies suggested that diabetes mellitus in Parkinson's disease is associated with its more severe progression and reduced efficacy of therapy[173,174]. We propose that the dysfunction of the autonomic nervous system, present in Parkinson's disease as well as individuals with diabetes mellitus[175], may be exacerbated when the two conditions co-occur, and could explain the high risk of death. Also, the failure to recognize symptoms of hypoglycemia due to a low sympathetic response may contribute to the mortality risk.

PDD patients were also less likely to have ischemic heart disease, in line with reports that patients with Parkinson´s disease have fewer VRFs[110]. However, heart failure, even though not significantly associated with PDD itself, was found to be associated with an increased risk of death in PDD patients. There is evidence that heart failure is a common cause of death in Parkinson's disease patients[176]. Even though the prognostic significance of the sympathetic denervation is not clear, autonomic dysfunction could contribute to the onset of heart failure[48,177]. Of note are also reports that some dopamine agonists used to treat Parkinson's disease increase the risk of heart failure[178].

Contradicting the lower prevalence of CVD in Lewy body dementias, we observed a higher burden of cerebrovascular diseases in DLB patients, as in a previous study using the same data[179]. A potential explanation is that this may be caused by the use of antipsychotic drugs, which is considered high in DLB patients, despite their hypersensitivity to them[180].

FTD patients are burdened by fewer CVDs, which is mainly explained by their lower age. Even though they were least likely to suffer from ischemic heart disease, it was associated with a doubled risk of death in this group of patients. Moreover, atrial fibrillation was linked to a three times increased mortality risk. A possible explanation can be that the diagnosis of FTD overshadows the need for treatment of ischemic heart disease and atrial fibrillation.

5.4 MANAGEMENT OF MYOCARDIAL INFARCTION IN PATIENTS WITH DEMENTIA (PAPER IV)

From the 525 patients who suffered an acute myocardial infarction after the diagnosis of dementia (mean age 82 years, 54% women), 86 had STEMI, 235 NSTEMI and 204 unspecified myocardial infarction. Twenty one per cent of patients (n=110) received an invasive procedure for the management of myocardial infarction (coronary angiography and / or PCI). This was highest among STEMI patients and lowest among patients with unspecified myocardial infarction (Figure 14).

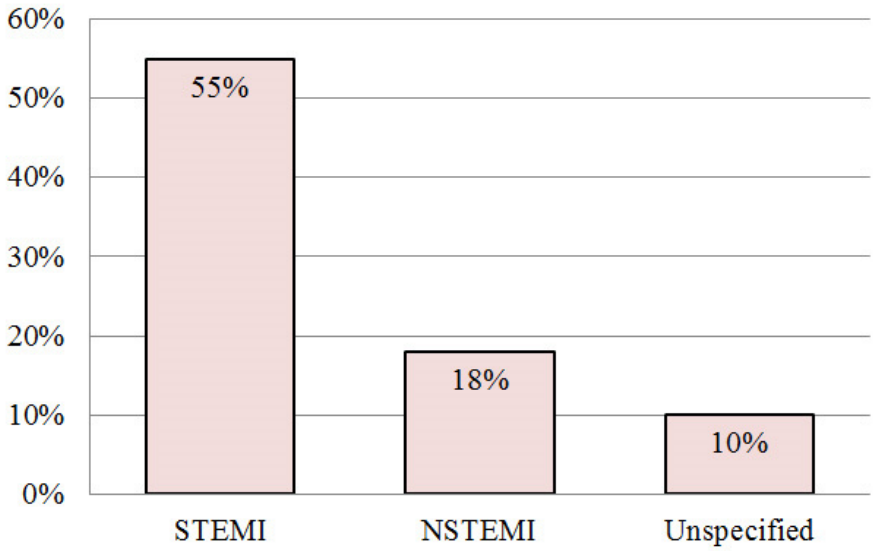

Figure 14 Use of invasive management stratified by type of myocardial infarction

STEMI, myocardial infarction with ST-elevation; NSTEMI, myocardial infarction without ST-elevation

Patients who received an invasive procedure were younger (78 vs. 83 years), less frequently women (41% vs. 57%), had a higher MMSE (24 vs. 21) and fewer comorbidities. In multivariate analysis (Table 5), lower age and higher MMSE were associated with receiving an invasive procedure, while there was no association of gender and comorbidity. Women had lower odds of being managed invasively in unadjusted analysis. The association became statistically non-significant, after controlling for type of myocardial infarction, age and MMSE.

The patients who received an invasive procedure survived longer (p=0.001; Figure 15). The use of an invasive procedure was associated with a lower risk of death, after adjusting for type and history of acute myocardial infarction, age, gender, type of dementia disorder, registration unit, comorbidity score (HR 0.35; 95% CI 0.21-0.59) or total number of drugs (HR 0.34; 95% CI 0.20-0.58).

Table 5 Associations of clinical characteristics with the use of an invasive procedure

	OR (95% CI)		
	Unadjusted	Model 1	Model 2
Age	0.89 (0.86-0.92)**	0.90 (0.86-0.94)**	0.89 (0.86-0.93)**
Female gender	0.52 (0.34-0.79)*	0.62 (0.37-1.06)	0.69 (0.41-1.16)
MMSE	1.18 (1.11-1.26)**	1.18 (1.10-1.26)**	1.19 (1.11-1.27)**
Comorbidity score	0.72 (0.60-087)*	0.80 (0.63-1.00)	
Total number of drugs	0.96 (0.91-1.01)		0.97 (0.91-1.03)

MMSE, Mini Mental State Examination; OR, odds ratio; CI, confidence interval
*** p<0.001; * p<0.05; ORs with 95% CI are derived from binary logistic regression and are estimates for associations of clinical characteristics with the use of an invasive procedure. Variables in Model 1: age, gender, MMSE, comorbidity score, type of myocardial infarction, history of myocardial infarction. Variables in Model 2: age, gender, MMSE, total number of drugs, type of myocardial infarction, history of myocardial infarction.*

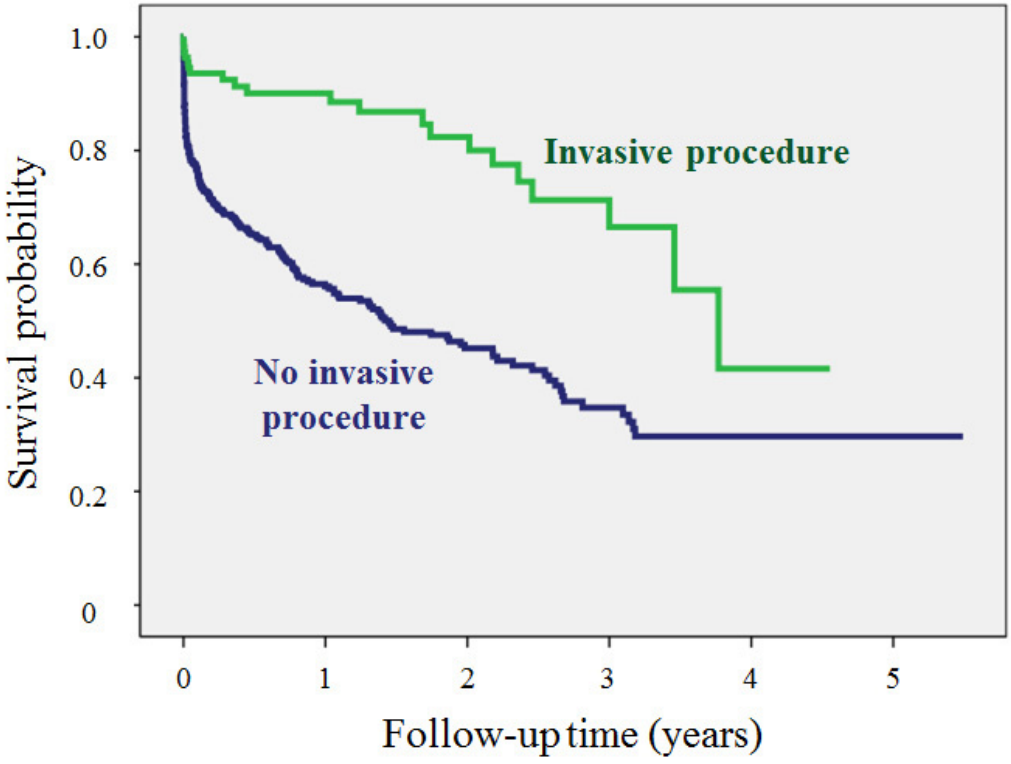

Figure 15 Kaplan-Meier survival curves, adapted from[181]

In Paper IV, we used data from the Swedish Patient Register, providing information about hospitalization for acute myocardial infarction after the diagnosis of dementia. As in other dementia cohorts[70,103], we found a low number of patients with myocardial infarction.

Patients who died out of hospital are not captured. Several cases may have not been recognized or registered, likely due to patients´ inability to describe symptoms, atypical presentation and high proportion of silent myocardial infarction[182,183].

This study suggests that the severity of cognitive impairment and higher age determine the management of myocardial infarction in patients with dementia. This may be explained by inadequate communication of symptoms, pre-hospital or in-hospital delays or personal judgement of physicians. In contrast with some literature[157,158], this study does not indicate that women had a lower chance of receiving optimal treatment. There was a lower frequency of women receiving treatment; however, this was explained mainly by their age, cognitive status and type of myocardial infarction.

The use of invasive procedures in this dementia cohort is lower than in the general population. Around 80% of octogenarians are treated invasively for STEMI and 20-30% for NSTEMI[184-188]. This reflects uncertainty, unknown benefits and lack of guidance to physicians when treating patients with dementia. Our study, investigating post-discharge survival of patients with dementia, suggests that patients with dementia benefit from the invasive management of acute myocardial infarction and supports its use in this patient group.

5.5 CARDIAC PARAMETERS IN YOUNG ADULTS AND THEIR BRAIN IN MID-LIFE (PAPER V)

The participants (Table 6) were on average 30 years old when they underwent echocardiography and 50 years old when they obtained brain MRI.

Table 6 Characteristics of the study participants (n=648)

Characteristic	Value
Women, n (%)	339 (52)
African Americans, n (%)	244 (38)
Years of education, mean ± SD	15.0 ± 2.3
Cardiac parameters, mean ± SD	
Left ventricular ejection fraction, % (n=297)	62.8 ± 7.4
Left atrial volume, ml/m^2 (n=406)	16.1 ± 4.2
Left ventricular mass, g/m^2 (n=627)	79.9 ± 18.4
Brain measures, mean ± SD	
White matter fractional anisotropy	0.3 ± 0.02
Gray matter volume, cm^3	518.5 ± 53.7
White matter volume, cm^3	467.0 ± 59.5
Total brain volume, cm^3	985.5 ± 107.2
Abnormal white matter volume, n (%)	
None	127 (20)
Little (≤ 0.3 cm^3)	246 (38)
High (> 0.3 cm^3)	275 (42)

SD, standard deviation

Higher left atrial volume was significantly associated with lower white matter fractional anisotropy, when controlled for age, sex, race/ethnicity, field center, years of education and intracranial volume (Table 7). This association remained statistically significant after adjusting for systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, fasting plasma glucose, smoking status, sedentary time, alcohol intake, ApoE ε4 allele (β -0.0023; 95% CI -0.0041; -0.0004; p=0.016). After we stratified the analysis by race/ethnicity, we observed the association only in African Americans. No cardiac parameter was associated with lower gray matter, white matter, total brain volume or higher abnormal white matter volume.

Table 7 Associations of cardiac parameters with brain measures

	White matter fractional anisotropy	Gray matter volume	White matter volume	Total brain volume
	ß (95% CI)			
LVEF	-0.0003 (-0.0022; 0.0017)	-0.763 (-3.103; 1.577)	1.512 (-1.285; 4.309)	0.749 (-2.582; 4.079)
LAV	-0.0026 (-0.0044; -0.0008)*	-0.042 (-2.187; 2.103)	-1.915 (-4.444; 0.615)	-1.957 (-4.952; 1.039)
LV mass	-0.0015 (-0.0030; 0.0001)	0.892 (-1.016; 2.800)	-0.027 (-2.147; 2.093)	0.864 (-1.647; 3.376)
	Abnormal white matter volume			
	None	Little ($\leq$ 0.3 cm^3)		High (> 0.3 cm^3)
	Reference	OR (95% CI)		
LVEF		0.94 (0.68; 1.30)		1.04 (0.74; 1.46)
LAV		0.73 (0.54; 0.97)		0.92 (0.69; 1.22)
LV mass		1.18 (0.92; 1.52)		1.15 (0.90; 1.49)

p=0.004

LVEF, left ventricular ejection fraction; LAV, left atrial volume; LV mass, left ventricular mass; OR, odds ratio; CI, confidence interval

ß is derived from linear regression and is a coefficient for an association of the cardiac parameter (independent variable) with a measure of aging brain (dependent variable). OR is derived from multinomial logistic regression and is a parameter for the association of the cardiac parameter with high or little abnormal white matter volume, when compared to no abnormal volume. Each cardiac parameter was transformed into Z score and entered into each model separately. All models are adjusted for age, sex, race/ethnicity, field center, years of education, intracranial volume.

Paper V, based on data from a prospective longitudinal study, indicates that larger left atrium in young adulthood may predict impairment in white matter integrity in mid-life. This is in line with previous studies on older adults that reported a link between enlargement of left atrium and indicators of brain pathology[189-191]. We did not find any association of left ventricular ejection fraction or left ventricular mass with any MRI markers, as opposed to previous studies on older adults[87,191-194].

Higher left atrial volume reflects diastolic dysfunction due to the exposure to VRFs and may be considered an early marker of cardiac disease. It is a predictor of atrial fibrillation and heart failure.[90,195-197] The relationship between left atrial volume and brain pathology may be explained by reduced brain perfusion due to lowered cardiac output or microembolism secondary to atrial fibrillation.

The data suggests an incipient impairment of white matter integrity at mid-life due to subclinical cardiac dysfunction. Decreased white matter integrity is possibly the first sign of pathological changes in the white matter, preceding development of white matter lesions, indicating a future risk of dementia[30,31,198]. Consistent with the view that prevention of dementia should start early in life, here we suggest that improving cardiac function in young adults may prevent their future brain disease. The association was strongest in African Americans, who have a larger burden of heart failure and dementia, when compared to Caucasians.[84,199] We propose that African Americans may be at a higher risk of brain pathology due to cardiac dysfunction.

6 METHODOLOGICAL CONSIDERATIONS

Generalizability of research findings is given by their internal (are the results true?) and external (do the results apply to other settings?) validity[200]. Validity is compromised by the presence of a systematic error – bias. There are several sources of bias, such as selection bias, misclassification and confounding.

6.1 SELECTION BIAS

Selection bias occurs when the chance that a person is included in the study is related to both the exposure and the outcome. It may be caused by non-participation, loss to follow-up or missing data. Selection bias due to non-participation is likely in Papers I-IV that are based on Swedish registers, which do not have a complete coverage in the country. On the other hand, selection bias due to loss to follow-up does not occur in Papers II-IV, where the outcome, all-cause mortality, was identified from a nationwide register. Missing data did not appear at random, but in particular among older and sicker patients.

The estimated coverage of SveDem is approximately 35%[201] and of RiksSvikt around 49%[202]. It has not been studied how the dementia patients in SveDem and heart failure patients in RiksSvikt differ from those who are not registered. As reported elsewhere[203], patients included in a quality register are more likely to be men, younger, generally healthier and have a higher socioeconomic status. This biases the generalizability of the results towards a healthier group of patients who have more contact with health care. This may lead to underestimation of the cardiovascular comorbidity in participants in Papers I-IV and the influence of CVD on their risk of death. The effect of invasive management of acute myocardial infarction on the risk of death may then be overestimated.

In order to fill in the gap in knowledge about CVD in women and minority groups, CARDIA study was designed to reflect the diversity in the population of the United States. At baseline, 52% of the participants were African Americans, 40% had less than 12 years of education, 30% reported regular smoking and the average body mass index was 24[143]. At the 25th follow-up exam, the retention was 72% from the surviving cohort; persons with more VRFs and African Americans were more likely to be lost to follow-up. Moreover, participants in the CARDIA MRI Sub-study had fewer VRFs compared to the remaining cohort. To conclude, this constitutes a selection bias, possible leading to underestimation of the effect of the cardiac parameters on brain health in Paper V.

6.2 MISCLASSIFICATION AND CONFOUNDING

Misclassification appears when a variable is not appropriately measured or does not sufficiently capture the construct of interest. Misclassification of the diagnoses of dementia and CVD in Swedish registers is a concern. The clinically made dementia diagnoses used in Papers I-IV have not been validated by a neuropathological examination, which is considered a gold standard for the diagnosis of dementia. When compared to autopsy records, studies from other countries suggest that the clinically made diagnosis of AD is correct in around 80% of cases[204,205], this number is likely to be lower in primary care units.

With reference to an expert review using criteria of the European Society of Cardiology, the validity of the diagnosis of heart failure in Sweden was suggested to be 82%. It is higher for patients treated in internal medicine (86%) and cardiology (91%)[206]. The diagnosis of acute myocardial infarction in the Swedish National Patient Register was suggested to have a high positive predictive value (98-100%)[141,207] and sensitivity of 77-91%[208,209]. However, these numbers can be lower for patients with dementia, who often present with atypical symptoms, have problems with communication and undergo less extensive diagnostic work-up.

A confounder is a factor associated with both the dependent and independent variable and is not on the causal pathway between them. An ideal way of preventing confounding is randomization. However, all 5 studies in this thesis are observational and there is a possibility that the adjustment in the analyses did not remove the effect of confounding variables, on which data was not collected. For example, in Papers I-IV, such factors may be lifestyle, genetic factors, socioeconomic and marital status, smoking, body mass index and type and location of the care center.

7 FUTURE PERSPECTIVES

The life expectancy is still increasing and it does not seem that we are approaching a limit of human lifespan[1]. It would be optimal if the extending lifespan was accompanied by an increasing "health span", the time lived without chronic diseases. The future will bring new insights into mechanisms underlying risk factors that are shared among age-related diseases. Possibly, we shall be able to halt the ageing process. We may stimulate regenerative capacity of cells, manipulate with epigenetic alterations underlying longevity, regulate pathways leading to autophagy and signaling cascades of senescence and programmed cell death.

Until this happens, we need to improve the care of patients affected with chronic diseases. Non-participation of patients with dementia in randomized clinical trials leads to lacking knowledge about the right treatment for their comorbid CVD. Physicians face insecurity, generally due to lacking guidelines and unknown benefits, which results in decision making based on their experience and intuition, rather than on evidence. This gap in knowledge could be filled in with the use of advanced analytical tools that allow causal inference from observational data based on large nationwide registers.

Environmental factors account for at least 70% of variation in lifespan and development of diseases[210]. Ideally, we should prevent / delay the onset of CVD and dementia, via promoting a healthy lifestyle starting as early in life as possible. Health inequalities related to individual socioeconomic position will probably be growing. Inequalities start early in life and are inevitable, but can be reduced by enhancing access to health care and strengthening educational and emotional development in order to improve health behavior[211,212]. The future needs to address complex causes of chronic diseases and find ways how to make bridges between their physical, biological, psychological and social aspects.

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