DISSERTATIONS IN
HEALTH
SCIENCES

Tuomas Kerola

The Interplay of Cardiovascular Burden with Cognition and Mortality

Publications of the University of Eastern Finland
Dissertations in Health Sciences

UNIVERSITY OF
EASTERN FINLAND

TUOMAS KEROLA

The interplay of cardiovascular burden with cognition and mortality

To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland
for public examination in the main auditorium of the
Päijät-Häme Central Hospital, Lahti, Finland,
on Friday, October the 21st 2011, at 12 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 73

Department of Internal Medicine
Institute of Clinical Medicine
School of Medicine, Faculty of Health Sciences, University of Eastern Finland
Kuopio
2011

Kopijyvä Oy
Kuopio, 2011

Distributor:
University of Eastern Finland
Kuopio Campus Library
P.O.Box 1627
FI-70211 Kuopio, Finland
http://www.uef.fi/kirjasto

ISBN (print): 978-952-61-0540-6
ISBN (pdf): 978-952-61-0541-3
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSNL: 1798-5706

Author's address: Department of Internal Medicine
Päijät-Häme Central Hospital
Keskussairaalankatu 7
FI-15850
LAHTI
FINLAND

Supervisors: Docent Raimo Kettunen, M.D., Ph.D.
Department of Internal Medicine,
Päijät-Häme Central Hospital
LAHTI
FINLAND

Docent Tuomo Nieminen, M.D., Ph.D., M.Sc. (Eng.)
Department of Internal Medicine
Päijät-Häme Central Hospital, Lahti, Finland
and Department of Pharmacological Sciences,
Medical School, University of Tampere
TAMPERE
FINLAND

Reviewers: Docent Mikko Syvänne, M.D., Ph.D.
Finnish Heart Association
HELSINKI
FINLAND

Docent Miia Kivipelto, M.D., Ph.D.
Aging Research Center
Karolinska Institutet, Stockholm, Sweden
and Institute of Clinical Medicine, Department of
Neurology, Univeristy of Eastern Finland
KUOPIO
FINLAND

Opponent: Professor Timo Strandberg, M.D., Ph.D.
Department of Health Sciences/Geriatrics,
Unit of General Practice, University of Oulu
and Oulu University Hospital
OULU
FINLAND

Kerola, Tuomas
The interplay of cardiovascular burden with cognition and mortality
University of Eastern Finland, Faculty of Health Sciences, 2011
Publications of the University of Eastern Finland. Dissertations in Health Sciences 73. 2011. 62 p.

ISBN (print): 978-952-61-0540-6
ISBN (pdf): 978-952-61-0541-3
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSNL: 1798-5706

ABSTRACT

Traditional cardiovascular risk markers in mid-life are harbingers of cognitive decline, Alzheimer's disease and vascular dementia later in life. Normal aging, co-morbidities and other changes connected to cognitive decline make the interpretation of the risk markers assessed in the elderly clearly more challenging. This is the incentive for finding new cardiovascular markers with a more consistent risk stratification capacity for cognitive decline.

The aim of the present study was to evaluate B-type natriuretic peptide (BNP), the Mini Mental State Examination (MMSE) score and echocardiographical measures together with established cardiovascular risk factors for their impact on cognitive decline and mortality in the elderly general population.

The thesis is based on the Kuopio 75+ health study, a prospective population-based stratified cohort study with 601 individuals, aged more than 75 years, from Kuopio, Eastern Finland. The participants were examined at baseline and a follow-up visit at 5 years. Cognitive function, cardiovascular history and cardiovascular risk markers, including BNP, were recorded for all participants, and echocardiography was carried out in a sub-population of 355 individuals. The mortality data is based on a follow-up of a median of 7.9 years. Of the echocardiographical measures, left ventricular (LV) mass, ejection fraction (EF) and mitral inflow pattern (E/A) were all connected to mortality. LV mass and EF moderately predicted cardiovascular mortality. Interestingly, an $E/A < 0.75$ was more connected to non-cardiovascular than cardiovascular mortality. The presence of dementive illness was more common among individuals with an $E/A < 0.75$. High-density lipoprotein was associated with EF, while BNP showed no connection to EF.

Among individuals with no dementive illness at baseline, cardiovascular markers were evaluated for their predictive power over mortality, cognitive decline and dementia during the follow-up. While traditional cardiovascular risk-markers and illnesses failed to predict cognitive dysfunction, BNP was a strong predictor of all cognitive end-points. In this sub-group an MMSE score of 18–23 together with BNP were both independent predictors of mortality; the latter also predicted cardiovascular mortality.

The present study supports the notion that cognitive function and cardiovascular risk are closely connected also among the elderly. BNP, a direct marker of left ventricular stress, is a superior predictor of cognitive decline and mortality when compared to traditional risk-factors. The connection of BNP with future dementia and cognitive decline serves as a basis for testing the impact of antihypertensive treatment in the prevention of cognitive impairment in those with elevated BNP.

National Library of Medicine Classification: WG 100, WM220, WT120, WT116, WG 141
Medical Subject Headings: Cardiology, Cognitive function, Aged, Echocardiography, Mortality, B-type natriuretic peptide

Kerola, Tuomas
Sydän-ja verisuonitautien riskitekijöiden vaikutus kuolleisuuteen ja kognition huononemiseen.
Itä-Suomen yliopisto, terveystieteiden tiedekunta, 2011.
Publications of the University of Eastern Finland. Dissertations in Health Sciences 73. 2011. 62 s.

ISBN (print): 978-952-61-0540-6
ISBN (pdf): 978-952-61-0541-3
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSNL: 1798-5706

TIIVISTELMÄ

Väestön ikääntymisen myötä muistisairauksien odotetaan yleistyvän maailmanlaajuisesti. Perinteisten sydän- ja verisuonisairauksien riskitekijöiden ilmeneminen keski-iässä on yhdistetty kognition huononemiseen ja Alzheimerin tautiin vanhusväestössä. Ikääntymiseen liittyvät elimistön muutokset ja iän myötä yleistyvät liitännäissairaudet vaikuttavat sydän- ja verisuonisairauksien riskitekijöihin ja vaikeuttavat näiden riskitekijöiden ja muistihäiriöiden yhteyden tulkintaa vanhusväestössä.

Tutkimuksemme tavoitteena oli arvioida B-tyypin natriureettisen peptidin (BNP) ja Mini Mental State Examination (MMSE) -tutkimuksen ennustearvoa kuolleisuuden, muistin huononemisen ja dementoivien sairauksien suhteen yhdessä perinteisten sydän- ja verisuonisairauksien riskitekijöiden kanssa. Toisena kiinnostuksen kohteena oli sydämen ultraäänitutkimuksessa saatavien mittaustulosten merkitys kuolleisuuden ennustajina sekä niiden yhteys BNP:hen ja muihin sydän- ja verisuonisairauksien riskitekijöihin.

Kuopio 75+ -tutkimus on prospektiivinen, ositettuun otantaan perustuva väestötutkimus, johon osallistui 601 yli 75-vuotiasta kuopiolaista henkilöä. Osallistujat tutkittiin, ja heidän kuolleisuuttaan seurattiin 7.9 (mediaani) vuoden ajan. Osallistujien laajat demografiset tiedot, sydän- ja verisuonisairaushistoria ja -riskitekijät sekä kognitiivinen suorituskyky olivat erityisen mielenkiinnon kohteena. BNP ja peruslaboratoriokokeet tutkittiin. Sydämen ultraäänitutkimus tehtiin 355 satunnaisesti valitulle osallistujalle. Viiden vuoden kuluttua lähtötilanteesta osallistujat kutsuttiin seurantakäynnille.

Sydämen ultraäänitutkimuksen parametreista vasemman kammion massa, ejektiofraktio (EF) ja pulssi-Doppler -tekniikalla määritetty mitraaliläpän sisäänvirtauskuvio (E/A) ennustivat kuolleisuutta seurannassa. Vasemman kammion massa ja EF ennustivat kohtalaisesti kuolleisuutta sydän- ja verisuonisairauksiin, kun taas E/A < 0.75 ennusti ennen kaikkea kuolleisuutta muihin kuin sydän- ja verisuonisairauksiin. Tämän lisäksi E/A < 0.75 assosioitui dementian ilmenemiseen. Pieni HDL-kolesteroliarvo oli yhteydessä EF:on, kun taas BNP:llä ei ollut yhteyttä siihen.

Sydän- ja verisuonisairauksien riskitekijöiden merkitystä kuolleisuuden, muistin huononemisen ja dementian ennustajana arvioitiin osallistujajoukossa, joilla ei ollut dementoivaa sairautta lähtötilanteessa. Perinteisillä sydän- ja verisuonisairauksien riskitekijöillä ei ollut yhteyttä muistin huononemiseen seurannassa, kun taas BNP ennusti merkittävästi kaikkia kognition huononemiseen liittyviä päätetapahtumia. BNP ja MMSE 18–23 ennustivat molemmat kuolleisuutta seurannassa. Kohonnut BNP liittyi itsenäisesti erityisesti sydän- ja verisuonitautikuolleisuuteen, kun taas MMSE 18–23 ei merkittävästi tätä ennustanut, kun tunnetut riskitekijät otettiin huomioon.

Tuloksemme vahvistavat sitä käsitystä, että sydän- ja verisuonisairaudet ja kognition huononeminen ovat kiinteässä yhteydessä keskenään myös vanhusväestössä ja niillä on itsenäinen merkitys kuolleisuuden lisääjinä. Tutkimuksessamme todettu BNP:n yhteys kognition huononemiseen ja dementian ilmenemiseen seurannassa tarjoaa mahdollisuuden tutkia verenpainelääkityksen vaikutusta muistihäiriön ilmenemiseen ja vaikeutumiseen potilailla, joilla on suuri BNP-pitoisuus.

Yleinen suomalainen asiasanasto: dementia, sydän-ja verisuonisairaudet, kuolleisuus, ikääntyneet, ultraäänitutkimus, kognitio

ACKNOWLEDGEMENTS

This study was carried out at Päijät-Häme Central Hospital and the University of Eastern Finland between 2008 and 2011. The basis for the study was established in 1998 in the city of Kuopio when the Kuopio 75+ study was commenced.

I wish to express my deepest gratitude to my supervisor, Professor Raimo Kettunen, for introducing me to this project. His supportive approach and thorough understanding of cardiovascular medicine has helped me immensely in carrying through this project. It has been a privilege to work under his supervision for these years. Docent Tuomo Nieminen has been invaluable in supervising the present thesis. His enthusiasm as well as scientific and statistical experience have served as a solid foundation for this project. I have thoroughly enjoyed our discussions about the project as well as issues outside the field of science.

Professor Raimo Sulkava is acknowledged for his vision in commencing the Kuopio75+ study and carrying out the collection of the study data. Professor Sirpa Hartikainen has made an immense contribution in following up the patients and has offered remarkable expertise in the field of geriatrics. Professor Olli Vuolteenaho from the University of Oulu is acknowledged for offering his deep comprehension of natriuretic peptides and cardiac physiology to this project.

I wish to thank Professor Mikko Syvänne and Docent Miia Kivipelto for their review of my thesis. In addition, Ms. Eeva Parviainen is acknowledged for the excellent linguistic revision of the original publications and the thesis.

I owe warm thanks to all of my colleagues at Päijät-Häme Central Hospital and Tampere University Hospital who showed interest in and support for this work. Especially, I would like to thank Dr. Olli Anttonen for his supportive and enthusiastic approach to the research and the present thesis. I express my warmest gratitude to Dr. Seppo Voutilainen and Dr. Tomi Kaukonen for the inspiring discussions in the field of cardiology and life in general.

I wish to express my gratitude to all of my friends and relatives. I would especially like to thank my godparents, Paavo and Marjatta Kerola, for their friendship and help in our everyday life.

I want to thank my parents Ilkka and Leila as well as my brothers Jaakko and Antti for their continuous love and support.

My warmest and dearest gratitude I express to my three wonderful children, Sophia, Nikolas and Mikaela, for making my life richer and definitely less boring. Above all, I would like to express my love and appreciation to my wife, Nina, for being there and sharing this life with me.

In appreciation of their financial support, I would like to thank Päijät-Häme Central Hospital, the Hilja and Onni Tuovinen Foundation, the Päijät-Häme Regional Fund of the Finnish Cultural Foundation (Kaisu and Antti Ravani Fund), the Finnish Medical Foundation, the Päivikki and Sakari Sohlberg Foundation and the Aarne Koskelo Foundation.

List of the original publications

This thesis is based on the following original publications, referred to in the text by the Roman numerals I–IV**:**

I Kerola T, Nieminen T, Hartikainen S, Sulkava R, Vuolteenaho O, Kettunen R. High-density lipoprotein is superior to B-type natriuretic peptide as a marker of systolic dysfunction in an elderly general population. Scandinavian Journal of Clinical and Laboratory Investigation 2009;69:865-872.

II Kerola T, Nieminen T, Sulkava R, Vuolteenaho O, Hartikainen S, Kettunen R. Inverted mitral inflow pattern in echocardiography among the elderly – a marker of non-cardiovascular mortality and cognitive dysfunction. International Journal of Cardiology, in press.

III Kerola T, Nieminen T, Hartikainen S, Sulkava R, Vuolteenaho O, Kettunen R. B-type natriuretic peptide as a predictor of declining cognitive function and dementia – a cohort study of an elderly general population with a 5-year follow-up. Annals of Medicine 2010;42:207-15.

IV Kerola T, Hiltunen M, Kettunen R, Hartikainen S, Sulkava R, Vuolteenaho O, Nieminen T. Mini-Mental State Examination Score and B-type Natriuretic Peptide as Predictors of Cardiovascular and Total Mortality in an Elderly General Population. Annals of Medicine; in press.

The literature review is partly based on the following review article:

Kerola T, Kettunen R, Nieminen T. The complex interplay of cardiovascular system and cognition: how to predict dementia in the elderly? International Journal of Cardiology 2011;150:123-129. An invited review.

Contents

ABBREVIATIONS

A	Atrial component of the Doppler-measured diastolic mitral inflow
ACE	Angiotensin converting enzyme
ACE-i	Angiotensin converting enzyme inhibitor
AD	Alzheimer's disease
ANOVA	One-way analysis of variance
ANP	Atrial natriuretic peptide
APOE	Apolipoprotein E gene
ARB	Angiotensin II receptor blocker
ASO	Arteriosclerosis obliterans
beta	Standardized regression coefficient
BMI	Body mass index
BNP	B-type natriuretic peptide
BSA	Body surface area
Ca	Calcium
Cr-Cl	Creatinine clearance
CI	Confidence interval
CRP	C-reactive protein
DSM-IV	Diagnostic and statistical manual for mental disorders, fourth edition
E	Early component of the Doppler-measured diastolic mitral inflow
EF	Ejection fraction
HDL	High-density lipoprotein
HF	Heart failure
HR	Hazard ratio
ICD-10	International classification of the diseases, tenth edition
IQR	Interquartile range

K2-EDTA	Ethylenediaminetetraacetic acid dipotassium salt
LAD	Left atrium diameter
LDL	Low-density lipoprotein
LV	Left ventricle
LVIDd	Left ventricular diastolic diameter
LVIDs	Left ventricular systolic diameter
mmHg	Millimetre of mercury
MMSE	Mini Mental State Examination
MR-proANP	Mid-regional pro-atrial natriuretic peptide
MI	Myocardial infarction
NPR	Membrane-bound natriuretic peptide receptor
NT-proANP	N-terminal pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PWTd	Posterior wall thickness at end-diastole
RAA	Renin-angiotensin-aldosterone
SD	Standard deviation
SWTd	Septal wall thickness at end-diastole
VaD	Vascular dementia

1 Introduction

At present, the risk of an individual to develop dementia over his or her lifetime is 20% for men and 33% for women (Herbert et al. 2003), and globally as many as one in four persons aged 85 years or older, representing the fastest-growing segment of the population, may suffer from Alzheimer's disease (AD) or another dementing illness (Ferri et al. 2005). The aging of the population is expected to make the incidence and prevalence of various types of dementia double every twenty years, amounting to a global figure of 81 million persons affected by the year 2040 (Ferri et al. 2005). With no curative treatment available, measures need to be taken to recognise the risk factor of dementia that can be modified.

The two most common forms of dementia, Alzheimer's disease (AD) and vascular dementia (VaD), have traditionally been classified as separate entities – AD was formerly considered a purely neurodegenerative process that causes cognitive dysfunction, whereas VaD was defined as cognitive impairment due to vascular diseases. It has been demonstrated recently that cardiovascular risk factors, such as diabetes, hypertension, dyslipidaemia and metabolic syndrome, are associated with not only VaD but also AD (Kivipelto et al. 2001; Kloppenborg et al. 2008; Xu et al. 2009).

Hypertension, hyperlipidaemia, and diabetes in middle age predispose to cognitive impairment assessed in later life (Kivipelto et al. 2001; Kivipelto et al. 2001; Kloppenborg et al. 2008). The impact of these risk factors on cognitive function is less clear when measured in the elderly (Kloppenborg et al. 2008). Treatment of the cardiovascular risk factors, such as hypertension and hyperlipidaemia, has been associated with better cognitive function in cross-sectional studies, but the results from prospective trials have been disappointing (McGuinness et al. 2009).

Cognitive dysfunction has been reported to be common among elderly heart failure patients, and the level of cognitive dysfunction has been shown to associate with the level of systolic dysfunction among heart failure patients (Zuccala et al. 1997). Natriuretic peptides, secreted from the chambers of the heart in response to elevated stress on the heart muscle, have been connected to cognitive function in a few cross-sectional trials among younger populations (Gunstad et al. 2006; Feola et al. 2007; Buerger et al. 2009). Echocardiography is widely used in diagnosing structural heart disease and dysfunction of the heart. Several echocardiographic measures are also connected to excess mortality in general populations (Levy et al. 1990; Gardin et al. 2001; Bella et al. 2002; Wang et al. 2003; Kardys et al. 2009), but data has not been similarly validated among the elderly.

Severe cognitive decline and dementing illness have a remarkable impact on mortality (Kelman et al. 1994; Larson et al. 2004), but the role of modest impairment is less clear (Fried et al. 1998; Stump et al. 2001; Nguyen et al. 2003; Strandberg et al. 2009). BNP has performed well as a risk marker of mortality in several high-risk groups including the elderly (Wallen et al. 1997; Kistorp et al. 2005). Despite the accumulating evidence concerning the pivotal role of cardiovascular burden in the development of cognitive dysfunction, the independent predictive power of MMSE and BNP as mortality predictors has not been studied previously.

2 Review of the literature

2.1 CARDIOVASCULAR RISK MARKERS AND COGNITION

2.1.1 Hypertension

Hypertension is generally accepted as the most potent risk factor of stroke (Kearney et al. 2005), and when suffered in mid-life, it has been consistently linked with impaired cognitive function later in life, irrespective of the definition of hypertension used or the length of follow-up (Kloppenborg et al. 2008). In contrast, the studies with elderly populations have demonstrated remarkable variation in terms of results – several have found no association between systolic or diastolic blood pressure and cognitive decline (Herber et al. 2004; Tervo et al. 2004), while one longitudinal study with a population aged over 65 years, which was also the study with the longest follow-up, found high systolic blood pressure to associate with vascular dementia (VaD), but not with Alzheimer's disease (AD) (Yoshitake et al. 1995). Furthermore, the Kungsholmen project with a cohort of subjects aged 75–101 years and an average follow-up of 6 years connected cognitive decline with high systolic blood pressure, low diastolic blood pressure and elevated pulse pressure (Qiu et al. 2003; Qiu et al. 2005). On the other hand, longitudinal studies with populations aged 75 years or older (Guo et al. 1996; Morris et al. 2001; Verghese et al. 2003) and over 85 years (Ruitenberg et al. 2001) have reported a connection between low blood pressure and impaired cognitive function.

There are several possible explanations for these seemingly contradictory findings regarding arterial pressure and cognition. The adverse effect of high blood pressure is explained by the established association between systolic blood pressure and endothelial function and atherosclerosis. Chronic hypertension causes vascular pathology, leading to cerebral hypoperfusion and hypoxemia, which appears to be the likely mediator for the harmful effects of hypertension on cognition. The possible pathophysiological mechanism behind the progression from chronic hypertension to regional hypoperfusion include microvascular degeneration with altered cerebral endothelium, the proliferation of vascular smooth muscle cells, basal lamina alterations, luminal narrowing and fibrosis. Dysfunction of the rennin-angiotensin-aldosterone (RAA) system or the nitric oxide pathways, both of which are key mechanisms in the development of chronic hypertension, has been linked with congnitive decline – both directly and through the development of the said vascular changes. Furthermore, studies on mice have suggested that the accumulation of amyloid β may be directly increased by the vascular changes induced by hypertension (Iadecola 2004).

Low blood pressure, especially during diastole, causes hypoperfusion and hypoxemia in the brain tissue, which in turn promotes ischaemic injuries and clinical dementia. Among the elderly, several co-morbidities may have a simultaneous effect on blood pressure – a previously hypertensive patient, for instance, can develop heart failure, atrial fibrillation or aortic stenosis, which then lowers the blood pressure. Moreover, it has become commonplace to use blood-pressure-lowering agents to treat a diversity of cardiovascular conditions, and elderly individuals are also prone to become dehydrated, which can, in itself, lower blood pressure detrimentally. Furthermore, it has been shown that blood pressure begins to lower 2–3 years before the clinical diagnosis of AD, and it further attenuates when the cognitive dysfunction deepens in AD patients (Verghese et al. 2003; Hanon et al. 2005; Qiu et al. 2005).

Epidemiological data from several studies with large cohorts indicate that the application of antihypertensive medications is connected with better cognitive function (Guo et al. 1999; Veld et al. 2001). A recent prospective cohort analysis of a large population of elderly male cardiovascular disease patients revealed that those who were on angiotensin II receptor blockers (ARB) were significantly less likely to suffer from AD than individuals treated with other types of antihypertensive medications. Furthermore, the admission to a nursing home and mortality were delayed among ARB users with pre-existing AD (Li et al. 2010). The use of lisinopril, which is the most common angiotensin-converting enzyme inhibitor (ACE-i), was found to have a beneficial effect on cognition, but this association was not as marked. The combined use of both an ACE-i and an ARB yielded the best prognosis with regard to cognition (Li et al. 2010).

ACE inhibitors can be divided into two categories according to their ability to penetrate the blood-brain barrier: captopril, fosinopril, lisinopril, perindopril, ramipril and trandolapril are potentially centrally active, while benazepril, enalapril, moexipril and quinapril are not able to cross the blood-brain barrier and are therefore defined as non-centrally active. A retrospective analysis from the Cardiovascular Health Study suggested that, as opposed to other antihypertensive agents, ACE inhibitors had a protective effect on cognition, but only with regard to substances with potential centrally active agents (Sink et al. 2009).

In the context of possible benefits with reference to cognitive measures and dementia prevention, randomised hypertension treatment studies on the elderly have yielded conflicting results (Applegate et al. 1994; Forette et al. 1998; Skoog et al. 2005; Peters et al. 2008). Only one of the studies, with the calcium-channel blocker nitrendipine as the study drug, indicated that antihypertensive drugs might be beneficial in preventing dementia among the elderly (Forette et al. 1998); the principal result of this study was based on 11 vs. 21 dementia cases over a follow-up of two years. A Cochrane database systematic review which included these four trials concluded that there is no convincing evidence to date from randomised controlled trials to the effect that lowering blood pressure in late life prevents the development of cognitive impairment and dementia in patients with no apparent prior cerebrovascular disease (McGuinness et al. 2009). A recent analysis from the ONTARGET trial comparing ARB, telmisartan and the ACE inhibitor ramipril, or the combination of these two, found no difference in cognitive decline between the groups. In the TRANSCEND sub-study of this trial, those intolerant to ACE inhibition were treated blindly with either placebo or telmisartan. Disappointingly, treatment with telmisartan did not have an impact on cognition during the follow-up of 5.3 years among 5,926 participants with diabetes or cardiovascular disease (Anderson et al. 2011).

It should be pointed out that none of the randomised trials conducted to date have included congnitive measures or a diagnosis of dementia as a primary endpoint. The dropout rates have also been high in many of the studies, which possibly negates the effect of the study drug on any cognitive aspects (Di Bari et al. 2001). Furthermore, as pointed out in the Cochrane review, the use of antihypertensive medication has also been common in the control groups, which may attenuate the true effect of the antihypertensive treatment on cognition (McGuinness et al. 2009). Another factor possibly downplaying the results is that the follow-up periods of the mentioned studies may have been too short to uncover the beneficial effects on cognition. Considering these methodological imperfections, it is obvious that randomised placebo-controlled trials using cognitive measures and diagnosed AD and VaD as primary endpoints are required, before the effect of antihypertensive treatment on cognition in the elderly can be properly estimated.

2.1.2 Hyperlipidaemia

A high plasma cholesterol level in mid-life is an undisputed risk factor for cognitive dysfunction later in life (Kivipelto et al. 2001; Kivipelto et al. 2002; Whitmer et al. 2005). On the other hand, the risk is also increased among individuals whose cholesterol levels decrease from mid-life to late life (Solomon et al. 2007). The Mediterranean diet, known for its favourable composition in regard to lipid metabolism and the reduction of cardiovascular disease, has been associated with a reduction in the risk for AD (Scarmeas et al. 2006).

Among the elderly, the association between lipids and cognition is far more obscure, with most studies demonstrating no association between cholesterol and cognition in late life and a few even connecting low cholesterol with cognitive dysfunction (Mielke et al. 2005). The full extent of the role of cholesterol in the pathophysiology of dementive illnesses remains to be elucidated. In experimental studies, cholesterol has been linked with several key aspects in the development of Alzheimer's disease. The production of amyloid β, an essential factor in the development of AD, has been connected to cholesterol (Figure 1), and cholesterol-lowering agents have been demonstrated to decrease amyloid β accumulation in guinea pigs (Fassbender et al. 2001), but not in humans (Hoglund et al. 2006). Furthermore, high total cholesterol can accelerate the atherosclerotic process, which in turn causes elevated levels of amyloid β protein in the brain of an AD patient and thereby aggravates the neurodegeneration (Bodovitz et al. 1996; Simons et al. 1998). Another pathway through which the atherosclerotic process initiated by dyslipidaemia can facilitate cognitive dysfunction is by causing strokes and silent infarctions.

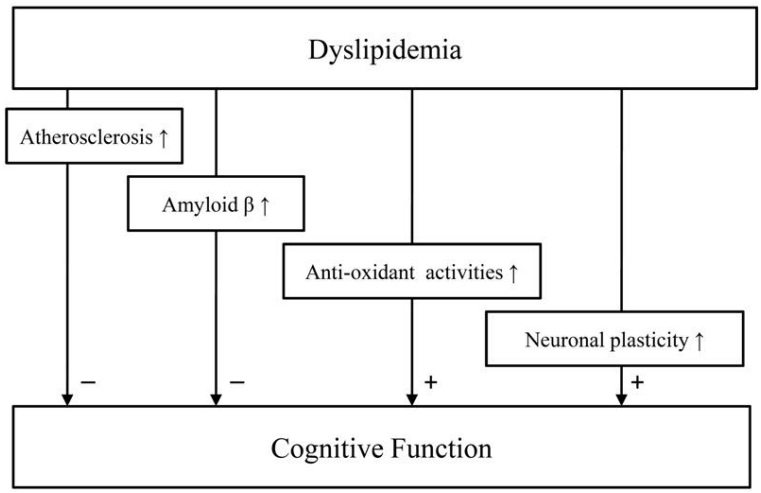


Figure 1. Suggested factors linking dyslipidaemia to cognitive capacity. Direction of effect is indicated with either a minus or a plus sign. Please see the text for details.

The apolipoprotein gene (APOE) ε4 allele is a known risk factor for cardiovascular disease (Nieminen et al. 2008) as well as mid-life and late-life Alzheimer's disease (Saunders et al. 1993). The carriers of this isoform among AD patiens experience a faster decline in their cognitive function (Cosention et al. 2008). Among cognitively normal individuals, carries of the APOE ε4 allele are at higher risk of developing a decline in their cognitive function if cardiovascular risk-factors are present (Caselli et al. 2011). Compared to the ε2 and ε3 alleles, ε4 is associated with down-regulation of the LDL receptor and

HMG-CoA, and these conflicting effects lead, in aggregate, to higher levels of LDL cholesterol (Mahley 1988), but it is not clear if this is the mechanism explaining the connection between APOE status and cognitive decline.

The fact that higher cholesterol has been found to have a seemingly protective effect on cognition among the elderly could be explained by the favourable impact of cholesterol on neuronal plasticity (Pfrieger 2003). Furthermore, weight loss is also common in AD and has been associated with lower blood lipids (Nourhashemi et al. 2008). A decrease in cholesterol from mid-life to late life, which has been shown to be a risk factor for dementia, might actually be a consequence of the pathological mechanisim that leads to dementive illness (Solomon et al. 2007) – the connection between high cholesterol and better cognitive function would then be flipside of the same phenomenon. It has been speculated that the anti-oxidant activities of the cholesterol could also potentially explain the association (Smith 1991). The systemic lipid metabolism and transport in human is separated from the central nervous system as the lipid particles are unable to cross the blood-brain barrier (Dietschy 2009). Cholesterol in peripheral circulation is bound to lipoproteins making any direct effect of plasma cholesterol on cognitive function unlikely (Hayashi 2011).

Cholesterol metabolism is closely associated with the progression of atherosclerosis and cardiovascular disease. Cholesterol-lowering with statins has been established as a successful stroke and cardiovascular disease prevention strategy (Pedersen et al. 1994; Sacs et al. 1996; Kerola et al. 2010), and several epidemiological studies have linked their use with a reduced risk of cognitive disorders both in mid-life and among the elderly (Jick et al. 2000; Haag et al. 2009). Two randomised placebo-controlled trials have been completed with focus on the efficacy of statin therapy in the prevention of cognitive deterioration among AD patients. In the larger of the two (n=640), atorvastatin was administered for 72 weeks to mild-to-moderate AD patients, with no significant benefits in terms of cognitive measures (Feldman et al. 2010). The results of the second trial, the CLASP (n=403), have not yet been published, but according to the lead investigator of the trial, there was no difference in primary or secondary outcomes between the simvastatin ajnd placebo groups (personal communication with Dr. Mary Sano, lead investigator of CLASP).

On the basis of the knowledge currently available, statin treatment cannot be recommended for the prevention of dementia. The study protocols of large statin trials from the last two decades have unfortunately not included the measurement of cognition (Pedersen et al. 1994; Sacks et al. 1996), and the potential benefits of statin therapy commenced in mid-life in regard to cognitive function remain to be addressed in future randomised trials.

2.1.3 Diabetes

Diabetes is exceedingly common among elderly populations – in 1996, the Rotterdam study reported a prevalence of 11.5% in a population aged 55 to 90 years (Ott et al. 1996), and recent data from the U.S. indicates that the prevalence of type II diabetes alone is as high as 23% among individuals aged over 60 years (U.S. Department of Health and Human Services 2005). Diabetes was first connected with cognitive impairment by Miles et al. as early as in 1922 when they demonstrated the inferior performance of diabetics in memory, arithmetic and psychomotor tests (Miles et al. 1922). Over the last two decades, multiple studies have investigated the potential association between diabetes and different forms of dementia as well as cognitive impairment among middle-aged individuals. Diabetes may contribute by accelerating several processes involved in the aging of the brain, such as oxidative stress, the accumulation of glycosylation and end products, microvascular dysfunction as well as changes in cerebral glucose and insulin metabolism

(Biessels et al. 2006). Regardless of some negative findings (e.g., Curb et al. 1999), an overwhelming body of evidence has established that diabetes, hyperinsulinaemia and insulin resistance among the middle-aged all predict dementia, AD and VaD (Luchsinger et al. 2004; Kloppenborg et al. 2008; Ronnemaa et al. 2008).

Studies with elderly populations have confirmed that diabetes continues to associate with cognitive decline after an individual reaches the age of 65 years (Luchsinger et al. 2007; Xu et al. 2009). Roberts et al. found that a diagnosis of diabetes per se was not a risk factor among subjects aged 70–89 years, whereas the complications of diabetes, the need for insulin treatment and an early onset of the diabetes all predicted cognitive impairment (Roberts et al. 2008). Furthermore, a history of severe hypoglycaemic episodes has been associated with an increase in the risk of dementia among type II diabetics aged over 55 (mean 65) years (Whitmer et al. 2009).

White matter changes are a common finding in brain imaging among elderly populations (de Leeuw et al. 2001), and this degenerative finding has been shown to associate with cognitive dysfunction, dementia and AD (Ylikoski et al. 1993; Kuller et al. 2003; Silbert et al. 2009). One recent study on a population with white matter changes reported diabetes to be the only cardiovascular risk marker predicting dementia (Verdelho et al. 2010).

There are several potential mechanisms connecting diabetes or hyperinsulinaemia with cognition (Figure 2). Diabetes is known to predispose to atherosclerotic cerebrovascular disease, which in turn may cause white matter changes of the subcortex as well as brain ischaemia and infarction. These manifestations are all well established as risk factors for dementia, and they are more commonly found in the brains of diabetics (Manschot et al. 2007). One cross-sectional study concluded that only hyperinsulinaemia, not type II diabetes, was independently connected to cognitive dysfunction (Vanhanen et al. 1999), while a prospective study among older women with a mean age of 66 years demonstrated that mildly hyperglycaemic subjects were at a higher risk of developing cognitive dysfunction as opposed to their normoglycaemic counterparts (Yaffe et al. 2004).

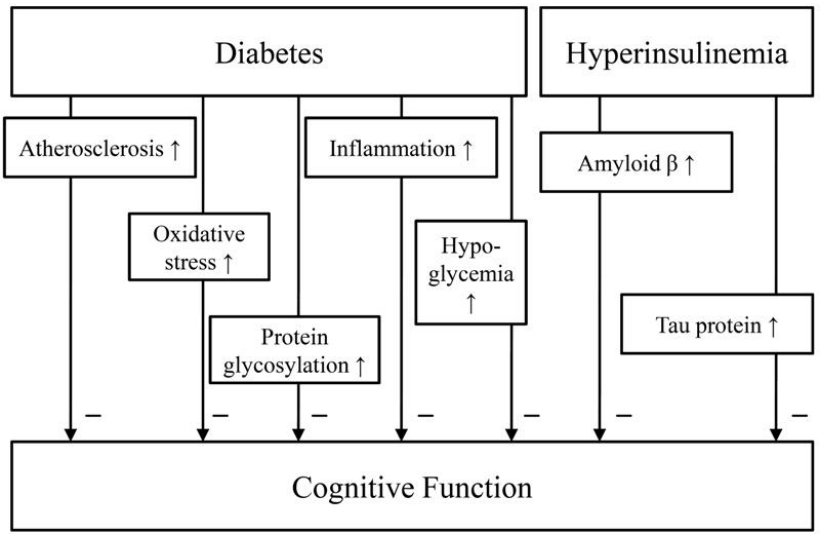


Figure 2. Suggested factors relating diabetes and hyperinsulinaemia to cognitive function. All the factors are risk factors for cognitive impairment. Please see the text for details.

Several studies have suggested that, in addition to atherogenesis, diabetes may have a more direct connection to dementia (Ott et al. 1996; Leibson et al. 1997), although there has been a deree of variation in the results (Ebly et al. 1995; Di Carlo et al. 2000). Oxidative stress or protein glycosylation can predispose diabetics to dementia (Biessels 1999). The accumulation of amyloid β and hyperphosphorylated tau protein, which are essential components of AD, has been linked with an insulin signalling defect (de la Monte et al. 2005). Hyperinsulinaemia may also have an adverse effect on the hippocampus, which is the part of the brain that is known to be the first to be affected in AD; the adverse effect may be mediated by insulin receptors in the hippocampus (Park 2001). Insulin-degrading enzyme in the brain lowers the extracellular level of amyloid β (Vekrellis et al. 2000), and this beneficial effect is inhibited by insulin (Farris et al. 2003). Furthermore, it has been demonstrated that hyperinsulinaemia increases amyloid β levels in the cerebrospinal fluid of healthy adults (Fishel et al. 2005). Diabetes is also associated with elevated concentrations of inflammatory factors – e.g., C-reactive protein (CRP), interleukin-6, tumour-necrosis factor-α and reactive oxygen species – which have also been shown to augment the risk of AD (Haan 2006).

Several studies have established an association between diabetes and cognitive decline, but the reports addressing the potential effect of diabetes treatment on cognition have been sparse and the results so far have not been promising. Two smaller trials demonstrated some benefit from more aggressive treatment of hyperglycaemia in elderly patients as regards cognition during a short follow-up of 6 (Naor et al. 1997) and 24 weeks (Ryan et al. 2006). The largest published trial, ADVANCE, assessed the benefits of intensive vs. standard glucose lowering therapy in more than 11,140 type II diabetics aged 55 years or older; during the 5-year follow-up, no significant difference in diagnosed dementia or cognitive decline was observed between the groups (Patel et al. 2008).

In theory, the insulin sensitizer rosiglitazone could have a favourable effect on cognition in AD, based on the mechanisms described above. It has shown promising results in early AD (Watson et al. 2005), although this only applied to carriers of APOE ε4 allele in another study (Risner et al. 2006). In a larger 6-month interventional trial where patients with mild to moderate AD were treated with rosiglitazone, however, no benefit was observed in regard to cognition regardless of the APOE status (Gold et al.). In fact, rosiglitazone has been withdrawn from clinical use on the European market due to the increased cardiovascular risk induced by its use (European Medicines Agency 2010).

As a conclusion, congnitive status has unfortunately not been followed routinely in large diabetes treatment trials. Therefore, the effect of longer-term treatment for hyperglycaemia on cognition remains to be settled.

2.1.4 Adiposity

In epidemiological studies, the most commonly used indicator for assessing excess body fat is the body mass index (BMI). The definition of “overweight" is a BMI of 25–29.9kg/m², and individuals with a BMI of 30 kg/m² or more are categorized as “obese”. However, central obesity measured by waist circumference would probably provide a more accurate estimate of adiposity than BMI (Mueller et al. 1991).

Obesity, overweight and central obesity in mid-life have been consistently linked with late-life cognitive impairment, Alzheimer’s disease and dementia (Gustafson et al. 2003; Kivipelto et al. 2005; Whitmer et al. 2005; Gustafson et al. 2009), but weight loss or lowering the BMI during follow-up has also been uniformly associated with a decline in cognitive function (Barrett-Connor et al. 1998; Stewart et al. 2005; Johnson et al. 2006). Knopman et al. found that the weight loss preceding dementia can start decades before the onset of clinical illness (Knopman et al. 2007).

Population-based results on the elderly have been conflicting regarding the association of adiposity with cognitive decline; on the one hand, lower BMI has been connected with cognitive dysfunction (Nourhashemi et al. 2003; Atti et al. 2008), but on the other, a study by Luchsinger et al. with a population aged less than 76 years revealed that the association between BMI and dementia resembled a U-shaped curve, with an older population demonstrating an inverse association (Luchsinger et al. 2007).

Metabolic syndrome has been established as an independent risk factor for cardiovascular disease and mortality, and it has also been associated with cognitive decline in several studies with varying populations (Yaffe et al. 2004; Yaffe et al. 2007). Two studies found a link between metabolic syndrome and cognitive decline only among older women (Vanhanen et al. 2006; van den Berg et al. 2007), while the impact on cognition was possibly attenuated among men (Vanhanen et al. 2006; van den Berg et al. 2007). The role of metabolic syndrome as a contributor in cognitive decline among older women was subsequently reaffirmed in a large study by Yaffe et al. (Yaffe et al. 2009).

The mechanisms at play in regard to the association between adiposity and cognitive impairment remain to be fully elucidated, but several plausible patwhways can be mentioned. As related risk markers for cerebrovascular disease and stroke, which predispose to dementia. adiposity, diabetes, dyslipidaemia and hypertension may have an indirect role in cognitive decline. Furthermore, hyperinsulinaemia is also common among individuals with adiposity and metabolic syndrome, and as discussed above, insulin and hyperinsulinaemia may play a direct role in the development of AD.

Several suggestions have been proposed as an explanation for the inverse association between adiposity and cognitive dysfunction among the elderly. Firstly, patients with AD begin to suffer from a memory deficit in the very early stages of the disease and can simply forget to eat, which leads to malnourishment. In fact, a recent study suggested that the weight loss during early AD is caused by a reduction in lean body mass rather than fat tissue (Burns et al. 2010). Dementia patients are physically less active than their healthy peers, which could explain the reduction in muscle mass, and insulin, as an anabolic substance linked with AD, may act as a mediator in this catabolic process occurring both in the musculature and in the brain (Burns et al. 2010).

Fat tissue is metabolically active and produces adipokines and cytokines. One of the adipokines, namely leptin, has been established to regulate food intake and energy balance, and the level of leptin in the circulation is directly related to the amount of fat tissue in the body (Friedman et al. 1998). In addition to its effect on the hypothalamic energy balance, leptin directly influences the hippocampus, which is the area of the brain that is first affected in AD (Harvey et al. 2006). Leptin administration has been discovered to enhance memory processing in mice – and in terms of the possible mechanisms behind this phenomenon, leptin is also known to regulate amyloid β levels (Fewlass et al. 2004). A study from the Framingham cohort revealed lower levels of leptin to be predictive of AD, dementia and the progression of pathological changes detected in magnetic resonance imaging during the follow-up, which suggests a direct protective effect of leptin on cognition (Lieb et al. 2009).

2.1.5 Smoking

Smoking has been well established as an independent cardiovascular risk factor, and it has also been linked with white matter changes, brain atrophy and a decline in perfusion (Meyer et al. 1999). Nicotine is an acetylcholine receptor antagonist and could potentially upregulate these receptors in the central nervous system (Murray et al. 2002). The amount of acetylcholine receptors is thought to decline with aging; a shortage of these receptors is evident in AD and other forms of dementia, making room for speculations as to a possible

favourable effect of nicotine, mostly consumed with tobacco, on cognition (Court et al. 2003).

In earlier studies, cigarette smoke was indeed suggested to have a protective effect against AD, but subsequent analyses have revealed this notion to have been largely due to selection bias (Hernan et al. 2008) and the influence of the tobacco industry as a source of financing for research (Cataldo et al. 2010). A meta-analysis of 23 prospective studies on the effect of smoking on dementia concluded that current smoking is clearly a risk factor for AD and possibly also for VaD and other forms of dementia – specifically, smokers were found to be at a 1.59-fold risk (95% confidence interval, 1.15–2.20) of AD and a 1.35-fold risk (0.9–1.59) of VaD in comparison to those who had never smoked (Peters et al. 2008). The result of this meta-analysis was confirmed and the impact of smoking on the occurrence of VaD clarified in a recent study (Rusanen et al. 2011). In a cohort of 21,123 individuals, heavy smokers had an over 2-fold risk for AD and VaD during a mean follow-up of 23 years.

2.2 B-TYPE NATRIURETIC PEPTIDE

2.2.1 B-type natriuretic peptide

Atrial natriuretic peptide (ANP) was discovered 30 years ago (de Bold et al. 1981). Later, the existence of B-type natriuretic peptide (BNP) was demonstrated (Sudoh et al. 1988). The discovery of these two cardiac peptides has launched a huge area of investigation concentrating on their synthesising, release and action. BNP was originally isolated from porcine brain extracts (hence the other name, brain natriuretic peptide), but its concentrations in the brain are actually very low or, in some species such as in the rat, even undetectable (Ogawa et al. 1990).

The cardiac natriuretic peptides are released from the chambers of the heart mainly due to stress of the myocardial wall, ANP from the atrium and BNP from the ventricles (Yasue et al. 1994). Myocardial ischaemia and endocrine modulation by other hormones and cytokines can also enhance peptide secretion. BNP is stored in myocytes as its precursor, proBNP, in the left atrium and ventricle. When secreted, proBNP is cleaved into two fragments, the active carboxyterminal fragment of BNP and the inactive N-terminal proBNP (NT-proBNP). The secretion and cleavage of proANP into inactive N-terminal proANP (NT-proANP) and ANP takes place in a similar fashion. The main source of active BNP is rapid gene expression with de novo synthesis of the peptide, and only small amounts are stored in the secretory granules. Normally, BNP is released from both the atrium and the ventricle, but in heart failure patients the main source of BNP seems to be the ventricular wall (Daniels et al. 2007; Richards 2007).

BNP is a natural antagonist of the (RAA) system, and its role as a fluid balance regulator seems to be of greater importance in patients under haemodynamic stress such as heart failure. Therefore, the physiological actions of BNP include a decrease in vascular resistance and central venous pressure as well as an increase in natriuresis. Thus, the resulting effect is an increase in cardiac output and decrease in blood volume. In addition, it inhibits the sympathetic nervous system and pathophysiological mechanisms, causing ventricular and vascular hypertrophy and remodelling. BNP is also known to have a beneficial effect on vascular endothelial dysfunction caused by atherosclerosis. (Vuolteenaho et al. 2005; Daniels et al. 2007; Richards 2007)

BNP has specific receptors situated in the cell membrane, mediating its biological actions. The mediating receptors are called "membrane bound natriuretic peptide receptors" (NPR). NPR-A preferentially binds ANP and BNP. NPR-C mediates the removal of natriuretic peptides from blood through the kidneys. BNP is cleared from

plasma by means of receptor-binding and proteolysis by a specific enzyme, neutral peptidase, whereas NT-proBNP is cleared through the kidneys without proteolysis. Due to differences in the clearance, the half-life of BNP in plasma is 20 minutes, whereas the half-life of NT-proBNP is 120 minutes and, similarly, the plasma values of NT-proBNP are approximately six times higher than BNP values (Vuolteenaho et al. 2005; Daniels et al. 2007; Richards 2007).

Levels of cardiac peptides can be measured from the blood and have been thoroughly investigated especially in the context of heart failure. ANP has a short half life and is unstable when stored. NT-proANP, BNP and NT-proBNP are known to be more stable and therefore better suitable for the assessment of cardiac patients. Women have higher levels of circulating NT-proANP, NT-proBNP and BNP, possibly due to the influence of oestrogen (Redfield et al. 2002; Loke et al. 2003). NT-proANP, BNP and NT-proBNP levels correlate positively with age, although the effect on BNP may be smaller (Redfield et al. 2002; Loke et al. 2003). In obese patients the natriuretic peptide levels seem to be lower (Mehra et al. 2004; Wang et al. 2004). Hyperthyroidism and anaemia are known to associate with natriuretic peptide levels. Higher heart rate seems to be correlated with lower levels of all three peptides. Renal insufficiency is associated hypertension, higher left ventricular mass and heart failure, all leading to elevated levels of natriuretic peptides. Renal insufficiency can also attenuate the clearance of the NT-proBNP and NPR-C, leading to falsely elevated levels of BNP and NT-BNP (Vuolteenaho et al. 2005; Daniels et al. 2007; Richards 2007).

2.2.2 B-type natriuretic peptide and echocardiographic measures

Normal BNP and NT-proBNP levels are known to exclude moderate to severe systolic dysfunction in untreated patients with symptoms suggestive of heart failure, and the measurement of plasma-BNP and p-NT-proBNP is widely recommended in this context (Tang et al. 2007). The level of BNP is also known to associate with the degree of diastolic dysfunction (Yamaguchi et al. 2004), level of left ventricular hypertrophy (Luchner et al. 2000), presence of atrial fibrillation (Ellinor et al. 2005) and the degree of heart valve disease (Daniels et al. 2007). In community screening, natriuretic peptides have been tested as a screening test for echocardiography, but their ability to identify patients with cardiac abnormalities in larger low-morbidity populations has been suboptimal (Vasan et al. 2002). Their use has been suggested to be cost-effective as a screening test for echocardiography among high-risk populations including the elderly (Heidenreich et al. 2004). BNP measures have also proven to associate inversely with the effective therapy of systolic heart failure, such as ACE inhibitors, ARBs and spironolactone (Inoko et al. 2001; Latini et al. 2002; Macdonald et al. 2004). This is probably due to a reduction in filling pressures and a reversal of pathological remodelling following a neurohormonal blockade of the RAA system. Changes in the level of natriuretic peptides, when treated with beta-adrenergic blockers, have been somewhat mixed, showing raised levels in the short term, but reduction in the natriuretic peptide levels in long-term treatment (Latini et al. 2002; Yoshizawa et al. 2004). Although some studies have suggested that the measurement of natriuretic peptides could be used in guiding a specific therapy of heart failure in clinical practice, this is not routinely recommended.

2.2.3 B-type natriuretic peptide as a prognostic tool among the elderly

Traditional cardiovascular risk factors, such as hypertension, dyslipidaemia, and obesity, seem to lose their value in predicting mortality for an elderly population and are often associated with a neutral or even better prognosis (Schupf et al. 2005; Oates et al. 2007; Takata et al. 2007). Natriuretic peptides are known to predict mortality in a wide variety of

cardiovascular diseases, including acute and chronic heart failure, myocardial infarction as well as stable and unstable coronary angina (Vuolteenaho et al. 2005; Daniels et al. 2007) (Wang et al. 2004). They have also performed well as a risk marker of mortality among the elderly, whereas CRP, another recently established cardiovascular risk marker for the general population, has failed to provide the same accuracy as a harbinger of mortality among aged populations (Wallen et al. 1997; Wallen et al. 1997; Strandberg et al. 2000; Kistorp et al. 2005).

2.2.3 Cognitive function and B-type natriuretic peptide

BNP has been reported to have an association with cognitive dysfunction in heart failure patients (Gunstad et al. 2006; Feola et al. 2007). In one study BNP levels were elevated in patients with subcortical vascular dementia, but not among age-matched controls or among patients with Alzheimer's disease (Kondziella et al. 2009). In another study increased levels of midregional pro-atrial natriuretic peptide, which is equivalent to NT-ANP as explained earlier, were found in patients with AD when compared to healthy controls (Buerger et al. 2009). Recently, it was shown that MR-proANP predicted the progression of mild cognitive impairment to AD in persons below the age of 72 years (Buerger et al. 2011). In one study with small group of patients with dementia, but no cardiovascular disease, BNP levels were significantly associated with cognitive function, whereas levels of ANP were normal (Naito et al. 2009).

2.3 MINI MENTAL STATE EXAMINATION SCORE

2.3.1 Mini Mental State Examination score

The Mini Mental State Examination (MMSE) score is a simple questionnaire originally developed for screening dementia (Folstein et al. 1975). It includes questions and problems in a number of areas: the time and place of the test, repeating lists of words, arithmetics, language use and comprehension, and basic motor skills. The MMSE score has a maximum of 30 points. An MMSE score of 18 to 23 points has been considered to suggest mild impairment and a score below 18 moderate to severe impairment of cognitive function. Individuals with dementia usually score less than 18 points (Bassuk et al. 2000). The MMSE score has been validated in a Finnish population, and 24 points correspond to the 5th percentile (Pulliainen et al. 2007).

2.3.2 Prognostic value of Mini Mental Examination score among the elderly

Severe cognitive decline, defined as an MMSE score of less than 18 points, and dementing illness have a remarkable impact on mortality (Kelman et al. 1994; Fried et al. 1998), but the role of modest impairment is less clear (Fried et al. 1998; Stump et al. 2001; Nguyen et al. 2003; Strandberg et al. 2009). Studies using an MMSE score of 18–23 as a definition of mild cognitive impairment (Bassuk et al. 2000; Strandberg et al. 2009) have found this criterion to be a significant predictor of mortality; the study by Bassuk et al. only in individuals aged less than 80 years. A study employing another measure of cognition, the Short Portable Mental Status Questionnaire, showed no predictive value for mild cognitive impairment (Stump et al. 2001). Previous studies examining the impact of modest cognitive impairment on mortality have often relied solely on the MMSE score to exclude those with different forms of dementing illnesses (Bassuk et al. 2000; Nguyen et al. 2003; Strandberg et al. 2009). Many participants with undiagnosed dementia and, therefore, compromised prognosis but who have a relatively preserved MMSE score have most probably been included in those studies.

2.4 ECHOCARDIOGRAPHY

2.4.1 Mitral inflow pattern

The filling of the left ventricle through the mitral valve in diastole happens in two phases. The pulsed Doppler technique can be used to measure the mitral inflow pattern. The early component is entitled the E wave and the late component the A wave. Aging is associated with left ventricular stiffening and the attenuation of the peak early diastolic filling velocity (E). Consequently, the atrial systole component of the diastolic filling (A) increases, the net result being a decrease in the echocardiographically measured E/A ratio (Dalen et al. 2010). Despite the introduction of tissue Doppler measures, the measurement of the E/A ratio is an integral part of estimating the diastolic function of the heart (Oh et al. 2006). Inverted mitral inflow (E/A <1.0) is used as a marker of the mildest form of left ventricle diastolic dysfunction, impaired relaxation with normal filling pressure (Oh et al. 2006). In the elderly, lower E/A limits—0.6 or, more commonly, 0.75—have been used for an inverted mitral inflow pattern (Bella et al. 2002; Redfield et al. 2003; Kardys et al. 2009).

Among populations of advanced age, the attenuation of the E/A ratio can be caused by many mechanisms not related to heart failure (Finucci et al. 1996; Bossone et al. 1999; Salerno et al. 2003; Gurudevan et al. 2007). The elderly often have an impaired ability to sense thirst (Waldreus et al. 2010), and chronic dehydration is common among the elderly, especially among cognitively impaired individuals (Morley 2002). Dehydration is known to co-exist with malignancies (Price). It decreases the filling pressure of the left ventricle, which attenuates the E wave and, consequently, lowers the mitral E/A ratio. Cognitive impairment and, in particular, dementive illnesses are known to have a remarkable impact on prognosis (Kelman et al. 1994; Larson et al. 2004). An inverted mitral inflow pattern is known to be more common among individuals with chronic lung disease or chronic pulmonary embolism (Bossone et al. 1999; Gurudevan et al. 2007). Liver failure is also known to cause intravascular hypovolaemia, and an inverted mitral inflow pattern has been shown to co-exist with liver cirrhosis (Finucci et al. 1996; Salerno et al. 2003).

2.4.2 Prognostic value of echocardiographic measures in the general population

Several large population-based studies have investigated the prognostic value of echocardiographic measures for mortality. Left ventricular mass (Levy et al. 1990; Gardin et al. 2001; Kardys et al. 2009) and ejection fraction (EF) (Fried et al. 1998; Redfield et al. 2003; Wang et al. 2003) have been demonstrated to predict mortality almost uniformly in several variably aged populations. Only one of the larger studies, remarkably the one with the shortest follow-up, showed no association with EF and mortality (Kardys et al. 2009). The diastolic left ventricular mitral inflow pattern recorded with the Doppler method has been connected to mortality in several studies. A restrictive mitral inflow pattern (E/A > 1.5) and an inverted mitral inflow pattern have also been linked to total and cardiovascular mortality (Bella et al. 2002; Kardys et al. 2009), with one of the studies finding the association only in men (Kardys et al. 2009). Diastolic dysfunction defined with a combination of pulsed Doppler and tissue Doppler techniques has been shown to predict total mortality in the general population (Redfield et al. 2003).

2.4.3 Left ventricular systolic function and lipids

Therapy with statins has been shown to diminish the occurrence of clinical heart failure in post-infarct patients (Pedersen et al. 1994; Sola et al. 2006), and it appears to have a positive effect on cardiac function in patients with non-ischemic cardiomyopathy (Sola et al. 2006) as well as in post-infarction patients with primary hyperlipidaemia (Talini et al. 2008). Low levels of HDL cholesterol have been shown to associate with decreased systolic

function in post-infarct patients and angina pectoris patients without obstructive coronary disease (Wang et al. 1999).

Hyperlipidaemia and low HDL cholesterol are known risk factors for atherosclerosis and coronary disease, which in turn can predispose to heart failure. In addition, HDL has potent anti-inflammatory and oxidation preventing properties (Banka 1996; Sviridov et al. 2008). HDL also has an anti-thrombotic and anti-adhesive effect on platelets and is known to protect endothelial function by stimulating endothelial nitric oxide synthase (Sviridov et al. 2008). Oxidative stress and endothelial dysfunction have been connected to heart failure and could partly explain the link between lipids and heart dysfunction (Bergamini et al. 2009).

The use of statins in heart failure patients could potentially be also harmful. Bacterial endotoxins (lipopolysaccharides) may be removed from circulation by lipoproteins. Lowering lipoprotein levels by statin treatment could potentially expose HF patients more to infection (Rauchhaus et al. 2000). Ubiquinone (coenzyme Q10) is a coenzyme in mitochondrial respiration in cardiac muscle. Plasma levels of ubiquinone have been inversely associated to excess mortality in HF patients. Statin treatment is known reduce the plasma level of ubiquinone (Molyneux et al. 2008). The effect of statin treatment on heart failure patients has been addressed in two large randomized prospective trials, CORONA (Kjekshus et al. 2007) and GISSI-HF (Tavazzi et al. 2008). Rosuvastin treatment for patients with symptomatic systolic heart failure (CORONA) or systolic and diastolic heart failure (GISSI-HF) was beneficial in neither of the studies. Based on these findings statin treatment for HF patients regardless of the ethiology is not recommended. In patients already on statin therapy with appropriate indication, discontinuation is not necessary if heart failure is diagnosed (Sadek et al. 2009).

3 Aims of the study

The impact of cardiovascular risk markers on cognition and mortality is known to alter with aging. The aim of the study was to evaluate the value of BNP along with established cardiovascular risk markers as a screening test for left ventricular systolic dysfunction, and as a predictor of cognitive decline and dementive illness during the follow-up. The independent prognostic power of BNP and MMSE, as well as echocardiographic measures in an elderly general population was also of particular interest.

The specific aims of the present study were:

1. To find predictors of attenuated left ventricular ejection fraction and systolic dysfunction in a population-based study of elderly people. (Study I)

2. To examine the value of echocardiographically measured left ventricular mass, ejection fraction and mitral inflow pattern in predicting cardiovascular and non-cardiovascular mortality in an elderly general population. (Study II)

3. To compare BNP with other cardiovascular risk markers for their value to predict the decline of cognitive function and new cases of dementia in an elderly general population free of dementia. (Study III)

4. To examine the power of BNP and mild cognitive impairment, defined as MMSE 18–23, as independent predictors of total and cardiovascular mortality together with established cardiovascular risk markers in an elderly general population free of severe cognitive impairment. (Study IV)

4 *Material and methods*

4.1 STUDY POPULATION

This study is a part of the larger population-based, multidisciplinary Kuopio 75+ health study focusing on the clinical epidemiology of diseases, medication, and functional capacity in elderly persons aged 75 years or older. The target population was a stratified random sample (n=700) of all residents of the City of Kuopio in Eastern Finland who were aged 75 years or more on 1 January 1998 (N = 4518). The cohort included 700 participants. Five persons could not be contacted, 79 refused to take part in the study, and fifteen died before the examination. The remaining 601 participants formed the study population.

4.2 BASELINE DATA

A trained nurse interviewed the participants at the outpatient clinic of the municipal hospital about their medical history and use of medicines and recorded the medicines they were currently taking. If a participant was unable to visit the study site, a nurse and geriatrician visited the home to perform the interview and examination. Medical records from the municipal health centre, home nursing service, local hospitals and Kuopio University Hospital were also available. Baseline clinical and demographic data and the NYHA class were also recorded. Diabetes was defined as a previous diagnosis of diabetes or a fasting plasma glucose level of 7.0 mmol/l or more. Data on other cardiovascular conditions were obtained from medical records. Blood systolic and diastolic pressures were measured twice, and the average of the measurements was recorded. Depression was screened using Zung's self-rating Depression Scale (Zung 1965).

Written informed consent was obtained from the study participants or their relatives as stipulated in the Declaration of Helsinki. The study was approved by the ethics committee of the Hospital District of Northern Savo and the Kuopio University Hospital.

4.3 LABORATORY MEASURES AND BRAIN IMAGINING

4.3.1 Standard laboratory measures

Complete blood count, creatinine, lipid profile, HDL-C, triglycerides and fasting blood glucose were measured once at Kuopio University Hospital after 12-hour fasting. All serum total cholesterol assays were analysed in the Kuopio University Hospital laboratory using standard enzymatic techniques. Creatinine clearance was calculated using creatinine, age and body weight according to Cockcroft-Gault's formula (Cockcroft et al. 1976). The estimation of low-density lipoprotein cholesterol was calculated using Friedewald's formula (Friedewald et al. 1972).

4.3.2 B-type natriuretic peptide

The blood samples for the analysis of BNP were withdrawn similarly with other blood samples into chilled tubes containing 1.5 mg K2-EDTA per mL blood after the patient had been in a supine position for 30 min at 8 a.m. The whole blood was centrifuged and plasma immediately frozen and stored at -70°C. BNP was extracted from plasma (Vuolteenaho et al. 1992). The radioimmunoassay protocol has been described previously for atrial natriretic peptide (ANP) (Vuolteenaho et al. 1992); the BNP assay was performed

with the same protocol. The BNP antiserum was raised in a rabbit against a carbodiimide conjugate of synthetic human BNP-32 (Bachem, Bubendorf, Switzerland) and bovine thyroglobulin (Sigma, St. Louis, USA) using methods published previously (Vuolteenaho et al. 1985). The sensitivity of the BNP assay was 0.5 pmol/L plasma. The within and between-assay coefficients of variation in the assay were <10% and <15%, respectively. With this method, the following plasma levels (mean ± SD) have been detected in healthy adults aged 20–55 years: BNP 6.25 ± 2.12 pmol/L.

4.3.3 Computed tomography and magnetic resonance imagining of the brain

Brain imaging either by computed tomography or magnetic resonance imaging was carried out for all participants with a suspicion of a dementing illness but no brain imaging in the medical history. The images were routinely analysed by a radiologist and an experienced neurogeriatrician.

4.4 MEASUREMENT OF COGNITIVE FUNCTION AND DIAGNOSING DEMENTIVE ILLNESSES

The study nurse used the Finnish version of MMSE score to screen for cognitive dysfunction. Dementia was diagnosed as AD, VaD, dementia with Lewy bodies, or dementia due to other medical conditions by an experienced neurogeriatrician according to the DSM-IV criteria and Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (McKeith et al. 1996). A clinical diagnosis of dementia was established, and the type of the dementia was determined in consensus meetings using all data available.

4.5 ECHOCARDIOGRAPHY

M-mode echocardiography was performed by a single experienced cardiologist (R.K.) with a Hewlett Packard Sonos 1000 ultrasound system (Hewlett- Packard Company, Andover, MA, USA) using a 2.5 MHz transducer. The measurements of the left atrium, septal wall thickness at end-diastole (SWTd), posterior wall thickness at end-diastole (PWTd), as well as left ventricular systolic (LVIDs) and diastolic diameter (LVIDd) were obtained and averaged from three to five cardiac cycles. M-mode measurements were performed according to the recommendations of the American Society of Echocardiography (Sahn et al. 1978). Two-dimensional (2D) left ventricular ejection fraction (EF) measurements in the apical long axis view were estimated by means of a single-plane ellipse formula (Folland et al. 1979). Left ventricular mass was calculated with the formula $0.8 \times 1.04[(LVIDd + PWTd + SWTd)^3-(LVIDd)^3] + 0.6)$ and indexed to the body surface area (Devereux et al. 1986). Significant valvular disease was defined as a mean pressure gradient across the aortic valve of 20 mmHg or more, as a valve regurgitation class II–IV or as mitral valve area of less than 1.5cm^2. The mitral inflow pattern was recorded by setting the pulsed Doppler sample volume at the mitral leaflet tips.

4.6 FOLLOW-UP VISIT AT FIVE YEARS

A total of 303 participants free of dementia at the baseline visit attended the follow-up visit at 5 years (Study III). Of the 161 participants missing, 133 expired during the study period and 28 either refused to continue the study or could not be contacted. The collection of baseline data and the diagnostic process for possible dementia, including MMSE score and brain imagining, were repeated.

4.7 FOLLOW-UP FOR MORTALITY

Mortality data were obtained from Statistics Finland, which is the national health register authority in Finland. There were no losses during follow-up. All deaths that occurred between March 1998 and November 2006 were recorded. Life span was calculated from the date of examination in 1998 to 30 November 2006. The causes of deaths were classified according to the Tenth International Classification of Disease (ICD-10), and codes I00–99 were classified as cardiovascular deaths. Other deaths were classified as non-cardiovascular.

4.8 PATIENT INCLUSION IN SUB-STUDIES

4.8.1 Study I

Echocardiography was performed for 355 randomly selected participants, who formed the final cohort of this study.

4.8.2 Study II

Echocardiography was performed for 355 randomly selected participants; a mitral inflow E and A wave could be recorded for 323 individuals who then formed the final cohort of this study.

4.8.3 Study III

Participants with diagnosed dementia (n=137) were excluded from this sub-study, and the final study population included 464 attendants. A total of 303 participants attended the follow-up visit at 5 years. Of the 161 participants missing, 133 expired during the study period and 28 either refused to continue the study or could not be contacted.

4.8.4 Study IV

Participants with 18 MMSE points or more were included (n=499) in this study.

4.9 STATISTICAL ANALYSIS

4.9.1 Ejection fraction, high-density lipoprotein and systolic dysfunction

Comparisons of baseline characteristics between the groups were performed with the aid of the t test for independent samples or the Mann-Whitney U-test for continuous variables, based on whether the distribution was Gaussian (Studies I, II and IV). In Study III the differences between the groups were tested with an ANOVA test for independent samples for continuous variables. A prior logarithmic transformation was performed for non-normally distributed variables. The χ^2-test was used for categorical data.

Binary logistic regression models were applied to determine the impact of various predefined independent variables on EF as a dichotomous variable (EF≤ or > 45%). One more logistic regression model was constructed for EF, using all the independent variables with significant associations in univariable models. Both the highly collinear lipid parameters total cholesterol and HDL cholesterol showed a significant association in separate models; however, only the one with the stronger association with EF (i.e., HDL cholesterol) was used in the final model. Hazard ratios (HR) for continuous variables were scaled to show the risk as the independent variable changes by one standard deviation

(SD). The testing scheme covered, separately, the entire study group (n=355) as well as participants with and (n=85) without (n=270) a previous heart failure diagnosis.

Linear regression models for the individuals with no prior diagnosis of heart failure (n=270) were applied to determine the impact of various independent variables on EF as a continuous variable. First, the standardised regression coefficients (beta) of variables listed in Table 2 were determined using separate linear regression models for each of these parameters. Finally, one more linear regression model was constructed for EF, using all the variables with significant coefficients in the initial models.

The impact of BNP and HDL cholesterol on EF was assessed with one-way analysis of variance (ANOVA) for BNP tertile groups, and a t–test for independent samples for the HDL groups below and at least 1 mmol/l. Sample size analysis was calculated for ANOVA with three equal-sized groups. If SD for EF is 0.2 in each group, the largest difference in mean EF between the groups 0.10, alpha 0.05 and beta 0.8, then roughly 80 patients are needed for each group.

4.9.2 Echocardiography and mortality

Due to the low number of individuals in group E/A > 1.5, statistical comparisons were made only between the groups E/A < 0.75 and E/A 0.75–1.5. Age- and sex-adjusted as well as pre-specified multivariable-adjusted Cox proportional hazards regression models for mortality were constructed to calculate HRs with 95% confidence intervals (CI) for EF, both as a continuous and as a dichotomized variable (pre-specified cut-off point 0.35), for left ventricular mass-index and E/A < 0.75. Analysis was repeated using cardiovascular as well as non-cardiovascular mortality as end-points. The age- and sex-adjusted Cox proportional hazards models for E/A < 0.75 vs. E/A 0.75–1.5, and for EF < 0.35 vs. EF ≥ 0.35, were used to construct cumulative survival curves for total, cardiovascular and non-cardiovascular mortality.

4.9.3 B-type natriuretic peptide and cognitive dysfunction

MMSE score at baseline and the change in MMSE score between the two visits (1998 and 2003) were studied as continuous variables. Univariable linear regression analysis was used to determine the impact of various baseline variables on the initial MMSE score and on the change in MMSE score over the study period (Table 6). Binary logistic regression models were applied to determine the impact of each baseline variable on the onset of dementia during the follow-up (Table 6). One more logistic regression model was constructed for new dementia cases using all the independent variables with a significant association in the univariable models. A separate regression model was adjusted to baseline MMSE score to determine the value of the variables for the prediction of dementia independent of MMSE score.

The baseline BNP levels of the participants are illustrated using box plots according to their status of dementive illness after the follow-up (Figure 3), with the differences between the groups assessed with ANOVA.

4.9.4 B-type natriuretic peptide, Mini Mental State Examination score and mortality

We used a Cox proportional hazards model with penalised splines (Greenland 1995) adjusted for age and sex to examine whether the association between mortality and the independent variables BNP and MMSE score changes in a nonlinear fashion across the full range of these independent parameters. A priori, we selected three degrees of freedom based on biological plausibility. Nonlinear models did not differ from linear models with

statistical significance using an analysis of deviance table with the χ^2-test, and for the rest of the tests, we applied linear models.

Cox proportional hazards regression models for total and cardiovascular mortality were constructed to calculate HR with 95% CI for BNP, the MMSE score, and the variables listed in Table 7. The proportionality assumption was checked for the main analyses based on correlations of survival rankings with Schoenfeld residuals; all covariates fulfilled this criterion. BNP and MMSE score were tested both as continuous and categorical variables (Table 8). Regarding the cut-off points for categorical formulations, we used the pre-specified <24 points for MMSE score, which was approximately the 20th percentile. Similarly, the 80th percentile for BNP (79.7 pg/ml) was used as a cut-off point to facilitate comparisons with earlier BNP studies (Bassuk et al. 2000; Strandberg et al. 2009). Cardiovascular risk markers and previous illnesses with a significant or near-significant ($p < .100$) stratifier capacity for mortality and cardiovascular mortality, separately, were used as covariates in multivariable Cox proportional hazards models. The analyses were repeated in pre-specified subgroups: participants with no diagnosed dementia (n=454) and participants with no previously diagnosed heart failure (n=376). HDL cholesterol and total cholesterol were highly collinear and both associated with mortality, but only the one with the stronger association, namely HDL cholesterol, was used in the Cox proportional hazards models.

4.9.5 Proportionality assumption, level of significance and statistical software

The proportionality assumption was checked for the main analyses based on correlations of survival rankings with Schoenfeld residuals; all covariates fulfilled this criterion. All tests were 2-sided, and $p < .05$ was considered significant. The data was analysed with SPSS release 15.0 for Windows (SPSS Inc. Chicago, Illinois).

5 Results

5.1 PREDICTORS OF ATTENUATED EJECTION FRACTION

The predictive power of clinical variables on ejection fraction was tested in a subgroup as described in **4.8.1.** Baseline data were analysed for the whole study population, and for subgroups with and without previously diagnosed heart failure separately. Participants with heart failure were older, and their use of cardiovascular medications and history of other cardiovascular diseases were more common. BNP levels were also higher among the heart failure group (Table 1).

5.1.1 Predictors of attenuated ejection fraction among participants with no history of heart failure

The variables tested independently for their impact on EF as a dichotomous variable are listed in Table 2. Age, HDL cholesterol and the use of an ACE inhibitor or an ARB were significantly connected to EF. Remarkably, BNP, creatinine clearance, sex, the use of a beta-blocker and previous myocardial infarct were not linked to EF. In the final logistic regression analysis, HDL cholesterol (HR=1.52; p=0.013) and age (HR=0.63; p=0.002) were the only variables to have an significant association with EF.

EF was also studied as a continuous variable. Variables in Table 2 were independently tested in linear regression analysis for their relation to EF in the group with no existing heart failure diagnosis (n=270). HDL cholesterol (beta = 0.123; p=0.04) and age (beta= -0.147; p=0.02) were the only variables to have an impact on EF. In the multivariable linear regression analysis, they were both independently associated with EF (HDL cholesterol, beta=0.127, p=0.04; and age, beta=-0.150, p=0.01).

5.1.2 Predictors of attenuated ejection fraction in the whole study population and among participants with a history of heart failure

HDL cholesterol as a continuous variable was associated with ejection fraction of less than 0.45 (HR=1.53; p=0.002) in the whole study population, but not among the heart failure patients. However, HDL cholesterol as a dichotomous variable (HDL cholesterol ≤ or > 1mmo/l) also showed a significant association in the latter group (HR=1.70; p=0.02).

HDL cholesterol was the only parameter to be significantly connected (beta = 0.109; p=0.04) to EF as a continuous variable in the whole study group, whereas for heart failure patients none of the parameters yielded a significant association.

Table 1. Characteristics of the participants with an echocardiographic examination. Data is provided for the whole study population and according to the history of heart failure, separately (Study 1).

	All (n=355)	No heart failure (n=270)	Heart failure (n=85)	p-value
Age in years, mean (SD)	80.3 (4.5)	79.6 (4.2)	82.7 (4.8)	<0.001
Women, %	72.7	72.6	72.9	NS
BMI, mean (SD)	26.3 (4.5)	25.9 (4.1)	27.7 (5.5)	0.002
Medication				
Regular medication, %	90.7	88.1	98.8	0.003
Beta-blocker, %	39.7	35.6	52.9	0.004
ACE-i/ARB, %	19.7	11.5	45.9	<0.001
Diuretics, %	36.1	23.3	76.5	<0.001
Ca-channel blockers, %	15.5	16.3	12.9	NS
Long-acting nitrates, %	29.3	20.4	57.6	<0.001
Statins, %	3.9	3.3	5.9	NS
Previous illnesses				
Previous MI, %	32.1	27.8	45.9	0.002
Hypertension, %	57.7	59.3	52.9	0.008
Heart failure, %	23.9	-	100	
Symptomatic ASO, %	10.1	8.1	16.5	0.027
Diabetes, %	20.6	16.3	34.1	<0.001
Previous stroke, %	13	10.7	20	NS
Smoking				
Non-smoker, %	75	74.1	77.8	NS
Ex-smoker, %	20.6	20.9	19.8	NS
Smoker, %	4.4	4.9	2.5	NS
Laboratory data				
Haemoglobin, mean (SD) g/l	133.9 (12.8)	133 (12.9)	134 (12.7)	NS
Cr-Cl, mean (SD) ml/min	51.5 (15.9)	52.7 (14.5	47.2 (19.7)	0.008
BNP, mean (SD) pg/ml	53.5 (59.2)	45.4 (44.5)	79.4 (87.0)	<0.001
Cholesterol, mean (SD) mmol/l	5.67 (1.18)	5.75 (1.15)	5.4 (1.2)	0.016
LDL cholesterol, mean (SD) mmol/l	3.53 (1.0)	3.59 (1.0)	3.30 (1.0)	0.034
HDL cholesterol, mean (SD) mmol/l	1.46 (0.41)	1.51 (0.4)	1.3 (0.39)	<0.001
Triglycerides, mean (SD) mmol/l	1.51 (0.80)	1.45 (0.75)	1.70 (0.90)	0.009
Echocardiographic parameters				
Ejection fraction, mean (SD)	0.54 (0.13)	0.55 (0.12)	0.52 (0.20)	NS
Systolic dysfunction EF ≤0.45, %	23.4	21.5	29.4	NS
LVMI, mean (SD), g/BSA m²	96.1 (34.6)	94.3 (35.2)	102 (32.0)	NS
Left ventricular hypertrophy, %	37.4	36.1	42.4	NS
Significant valvular heart disease, %	22.8	19.6	32.9	0.011

Left ventricular hypertrophy was defined as a left ventricular mass index > 95 g /m² for women and > 115 g/m² for men; significant valvular disease was defined as a mean pressure gradient across the aortic valve > 20 mmHg, valve regurgitation class II–IV, or mitral valve area < 1.5 cm².

5.1.3 Association of B-type natriuretic peptide and high-density lipoprotein cholesterol with other echocardiographic findings

The presence of significant valvular disease and left ventricular hypertrophy were tested as dichotomous variables in the total study population. BNP was clearly associated with significant valvular disease (HR=1.557; p<0.0001), but not with left ventricular hypertrophy (HR=1.093; p=0.262), whereas HDL cholesterol did not show any association with either of the variables. In order to exclude the possible effect of statin treatment, the analyses concerning HDL cholesterol were repeated without statin users (n=14). This did not produce any significant changes in results (data not shown).

Table 2. Binary logistic regression analysis presenting odds ratios and their significance of clinical variables for their association with ejection fraction as a dichotomous (≤ or > 0.45) variable; and, similarly, linear regression analysis, standardised regression coefficient (beta) and their significance, with ejection fraction as a continuous variable (Study I)

	EF ≤ or > 0.45		EF	
	HR	p-value	beta	p-value
Age	0.65	0.002	-0.147	0.015
Sex	0.65	0.175	-0.102	0.095
BMI	1.17	0.302	-0.038	0.538
Smoking	0.25	0.679	-0.06	0.334
NYHA class	0.51	0.126	-0.044	0.498
Diabetes	1.28	0.561	0.009	0.887
Hypertension	1.12	0.683	0.025	0.686
Previous MI	1.43	0.305	0.062	0.311
Symptomatic ASO	0.92	0.882	0.011	0.856
Previous stroke	0.67	0.245	-0.114	0.061
Heart rate	1.24	0.306	-0.04	0.511
Haemoglobin	0.88	0.95	-0.001	0.984
Creatinine clearance	1.31	0.13	-0.028	0.646
Cholesterol	1.43	0.025	0.093	0.126
LDL cholesterol	1.24	0.16	0.059	0.338
HDL cholesterol	1.51	0.013	0.123	0.043
Triglycerides	1.07	0.584	-0.001	0.985
BNP	1.09	0.594	0.022	0.718
Systolic BP	1.35	0.056	0.092	0.133
Diastolic BP	0.84	0.786	0.038	0.542
ACE-i/ARB	0.23	0.046	0.114	0.06
Other cardiovascular drugs		>0.200		>0.200

5.2 MORTALITY PREDICTING POWER OF ECHOCARDIORAPHIC PARAMETERS IN AN ELDERLY POPULATION

The associations of echocardiographic measures with total, cardiovascular and non-cardiovascular mortality were studied in a subgroup of the participants as described in

Table 3. Baseline characteristics of the participants presented according to their mitral inflow E per A ratio (Study II)

	E/A			
	<0.75	**0.75-1.50**	**>1.50**	**p-value**
Characteristics	n=151	n=155	n=17	
Age in years, mean (SD)	80.1(4.4)	80.1(4.4)	81.2(4.9)	0.910
Women, (%)	75.5	76.8	58.8	0.893
RR, systolic, mean (SD), mmHg	152.0(23.7)	153.4(23.2)	146.7(28.6)	0.588
RR, diastolic, mean (SD), mmHg	77.9(10.5)	75.8(10.8)	74.4(11.8)	0.089
Heart rate, mean (SD), beats/min	67.1(10.2)	67.9(14.0)	68.4(17.3)	0.818
NYHA class, mean (SD)	1.86(0.74)	1.87(0.74)	1.71(0.91)	0.902
BMI, mean (SD)	26.8(4.97)	26.4(4.45)	25.1(3.99)	0.497
MMSE score, mean (SD)	23.0(7.6)	23.7(7.0)	25.7(4.1)	0.449
Echocardiographic measures				
EF, mean (SD)	0.53(0.13)	0.56(0.11)	0.52(0.17)	0.012
LV mass index, mean (SD), g /BSA m^2	125.3(47.4)	121.1(50.8)	130.1(57.6)	0.497
LVIDd, mean (SD), cm	4.74(0.87)	4.71(0.97)	4.84(0.82)	0.841
LAD/BSA, mean (SD), cm	2.20(0.38)	2.30(3.57)	2.61(0.37)	0.018
Valvular heart disease, %	13.2	23.9	41.2	0.019
E/A, mean (SD)	0.62(0.078)	0.94(0.15)	2.05(0.47)	
Laboratory parameters				
Haemoglobin, mean (SD), g/l	134.6(13.1)	132.2(12.4)	133.5(13.6)	0.096
Creatinine clearance, mean (SD), ml/min	52.6(16.6)	52.3(15.3)	48.9(15.4)	0.904
Cholesterol, mean (SD), mmol/l	5.75(1.20)	5.82(1.16)	5.48(1.27)	0.626
HDL cholesterol, mean (SD), mmol/l	1.43(0.38)	1.53(0.43)	1.41(0.39)	0.018
BNP, mean (SD), pg/ml	35.0(36.7)	54.2(57.4)	67.4(42.0)	0.001
Medication				
Beta-blocker, %	33.8	45.2	47.1	0.047
ACE-i/ARBs, %	13.2	18.1	29.4	0.273
Diuretics, %	38.4	29	23.5	0.091
Ca-channel blockers, %	13.9	14.2	17.6	1.000
Statins, %	4	5.8	0	0.598
Previous illnesses				
Previous MI, %	33.1	31.6	32.2	0.808
Hypertension, %	55	58.1	58.8	0.483
Heart failure, %	21.2	18.7	17.6	0.344
Diabetes, %	21.2	15.5	23.5	0.237
Previous stroke, %	13.2	11	17.6	0.332
Dementive illness, %	25.2	14.2	5.9	0.011

Comparisons between the groups were performed with the aid of the t test for independent samples or the Mann - Whitney U-test for continuous variables, based on whether the distribution was Gaussian. The χ^2-test was used for categorical data.

detail in **4.8.2**. During a median follow-up period of 8.4 years (interquartile range, [IQR] 8.2–8.6) for survivors and 7.6 years (3.7–8.4) for the whole study population, 177 (54.8%) participants expired, producing an annual mortality rate of 9.0%. The cause of death was cardiovascular in 82 (46.3%) cases – malignancy with 26 (14.7%), infection with 15 (8.5%) and dementia-related reasons with 35 (19.8%) deaths being the other common causes. Due to the small number of participants with an E/A ratio of > 1.5 (n=17), comparisons were made between the individuals with E/A < 0.75 and E/A 0.75 – 1.5. Participants with an E/A ratio of <0.75 as compared to those with an E/A ratio of 0.75–1.5 had a lower ejection fraction, and significant valve disease was less common. BNP and HDL cholesterol were significantly lower, and there was a trend towards a higher frequency of the use of diuretics. There were no differences in previous illnesses between the groups apart from dementive illnesses, which were more common among participants with an E/A ratio of <0.75 (Table 3).

5.2.1 Left ventricular mass and mortality

The left ventricular mass index predicted total and cardiovascular mortality in all the models applied (Table 4). It had no connection to non-cardiovascular mortality.

5.2.2 Ejection fraction and mortality

EF as a continuous variable showed no association with total, cardiovascular or non-cardiovascular mortality. There was a trend towards higher total, cardiovascular and non-cardiovascular mortality if EF was dichotomised at 0.35 (Table 4).

5.2.3 Inverted mitral inflow pattern and mortality

An E/A ratio of < 0.75 was associated with total mortality in age- and sex-adjusted as well as the fully adjusted multivariable model. E/A < 0.75 showed no predictive value in similar models with cardiovascular mortality in either model, but it was a strong predictor of non-cardiovascular mortality in both the age- and sex-adjusted as well as the multivariable model (Table 4).

Table 4. Hazards ratios (HR), 95% confidence intervals (95% CI) and p-values for total, cardiovascular and non-cardiovascular mortality during a median follow up of 7.6 years according to baseline echocardiography measures (Study II)

	Total mortality		**Cardiovascular mortality**		**Non-cardiovascular mortality**	
Age and sex-adjusted	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
E/A < 0.75	1.54 (1.14-2.07)	0.004	1.24(0.80-1.91)	0.336	1.86(1.24-2.80)	0.003
EF	0.89(0.78-1.03)	0.132	0.91(0.75-1.11)	0.335	0.88(0.72-1.08)	0.232
EF <0.35	1.52(0.96-2.41)	0.073	1.66(0.90-3.06)	0.103	1.38(0.69-2.77)	0.366
LV mass index	1.22(1.05-1.34)	0.010	1.35(1.16-1.64)	< 0.001	1.00(0.82-1.28)	0.928
Multivariable adjusted						
E/A < 0.75	1.55(1.10-2.19)	0.013	1.31(0.78-2.22)	0.304	1.81(1.13-2.89)	0.013
EF	0.91(0.78-1.07)	0.266	0.95(0.76-19)	0.676	0.87(0.70-1.09)	0.239
EF <0.35	1.37(0.77-2.41)	0.282	1.40(0.64-3.02)	0.355	1.43(0.61-3.33)	0.408
LV mass index	1.22(1.05-1.42)	0.012	1.42(1.16-1.73)	< 0.001	1.00(0.78-1.35)	0.879

5.3 B-TYPE NATRIURETIC PEPTIDE AND COGNITIVE FUNCTION

The association of BNP with cognitive dysfunction and the incidence of dementia during follow-up was examined in a subgroup of participants as described in **4.8.3**. Baseline data according to BNP tertiles is presented in Table 5. The participants with a higher level of BNP were more likely to be older and have a history of heart failure, atrial fibrillation or stroke than those with a lower level of BNP. Systolic and diastolic blood pressures were lower among the participants with high BNP.

5.3.1 Association of clinical correlates with baseline cognitive function

Lower baseline MMSE score was connected to previously diagnosed heart failure and stroke as well as higher NYHA class, higher resting heart rate, lower creatinine clearance, lower HDL cholesterol and higher BNP. In addition, the MMSE score at baseline was associated with age and the duration of education. No significant association was found between baseline MMSE score and total cholesterol, smoking, diagnosis of hypertension, sex, diabetes, BMI, or systolic or diastolic blood pressure (Table 6).

5.3.2 Predictors of decline in Mini Mental State Examination score

The change in MMSE score during the follow-up of five years was, on average, -1.43 (SD 4.95) points. BNP was the only variable to have an impact on the decline in MMSE score during the follow-up. When adjusted to the level of baseline MMSE score, BNP continued to predict the decline in MMSE score. The traditional risk factors for cognitive decline, such as age, education, smoking, baseline MMSE score or cardiovascular risk markers or illnesses, showed no association with a declining MMSE score (Table 6).

5.3.3 Predictors of newly diagnosed dementias during the follow-up

During the follow-up visit, 59 new cases of dementia were detected. Using univariable logistic regression, the variables predicting the incidence of dementia during the follow-up were age, a diagnosis of hypertension, baseline MMSE score and BNP (Table 6). A multivariable regression model was developed for the above-mentioned significant variables. The duration of education, hypertension and BNP were independent predictors of new cases of dementia, while age lost its significance in the multivariable model. The multivariable model was additionally adjusted to the baseline MMSE score (Table 7).

Table 5. Baseline characteristics and drug treatment in all participants attending the 5-year follow-up visit according to their B-type natriuretic peptide tertiles. (Study III)

	BNP pmol/L			
Characteristics	**<23.5**	**23.5-53.7**	**>53.7**	**p-value**
Age in years, mean (SD)	78.6 (3.4)	79.8 (4.2)	81.3 (4.6)	<.001
Women, %	71.9	70.8	74.2	NS
BMI, mean (SD)	27.3 (4.3)	26.4 (4.5)	25.7 (4.0)	0.007
MMSE, median (IQR)	27 (25-29)	28 (25-29)	26 (24-29)	NS
MMSE <24 points, %	13.7	18.2	23.2	0.014
Education in years, mean (SD)	6.8	7.1	7.1	NS
Zung's depression scale, mean (SD)	38.8 (8.6)	39.1 (7.3)	40.2 (8.0)	NS
Medication				
Regular medication, %	84.3	88.3	96.7	0.001
Beta-blocker, %	28.1	40.9	64.9	<.001
ACE-i/ARBs, %	15	17.5	29.8	0.003
Diuretics, %	34	24	47.7	<.001
Ca-channel blockers, %	19	20.1	14.6	NS
Statins, %	3.9	7.1	3.3	NS
Oral diabetes medication, %	5.9	7.1	9.3	NS
Insulin, %	3.3	3.9	4.0	NS
Previous illnesses				
MI, %	26.8	35.7	34.4	NS
Hypertension, %	58.2	63.6	62.3	NS
Heart failure, %	14.4	16.2	43.0	<.001
Atrial fibrillation, %	3.9	10.4	31.1	<.001
Diabetes, %	21.6	15.6	24.5	NS
Stroke, %	6.5	7.1	17.2	0.014
Smoking				
Non-smoker, %	69.9	74.0	77.5	NS
Ex-smoker/Smoker, %	30.1	26.0	22.5	NS
Systolic RR, mean (SD), mmHg	151.9 (22.8)	157.1 (24.3)	149.9 (25.0)	0.026
Diastolic RR, mean (SD), mmHg	78.5 (9.54)	77.6 (10.2)	73.7 (11.8)	0.037
Laboratory data				
Haemoglobin, mean (SD), g/l	135. 2 (12.6)	133.6 (11.8)	131.7 (13.5)	NS
Cr-Cl, mean (SD), ml/min	56.4 (15.1)	54.8 (16.3)	47.2 (13.3)	<.001
fP-gluc, mean (SD), mmol/l	5.7 (1.34)	5.5 (1.13)	5.7 (1.52)	NS
Lipids				
Cholesterol, mean (SD), mmol/l	5.9 (1.21)	5.73 (1.18)	5.45 (1.21)	0.005
LDL cholesterol, mean (SD), mmol/l	4.08 (1.06)	3.89 (1.02)	3.74 (1.02)	NS
HDL choletesterol, mean (SD), mmol/l	1.46 (0.4)	1.56 (0.40)	1.41 (0.43)	0.009
Trigly, median (IQR), mmol/l	1.47 (1.0-2.0)	1.25 (0.9-1.6)	1.29 (1.0-1.8)	0.038

Table 6. Associations of clinical variables with baseline MMSE, decline in MMSE and new cases of dementia in five-year follow-up (Study III)

	Baseline MMSE		Decline of MMSE		New Dementia Cases	
	beta	**p value**	**beta**	**p value**	**HR (95% CI)**	**p value**
Age	-0.335	<.001	0.056	0.348	1.51 (1.14-2.11)	0.006
Sex	0.077	0.100	0.035	0.562	0.82 (0.42-1.58)	0.547
BMI	-0.018	0.696	-0.011	0.861	0.96 (0.72-1.30)	0.748
Education in years	0.392	<.001	0.006	0.921	0.48 (0.32-0.75)	<.001
Smoking	0.088	0.060	-0.009	0.878	2.07 (0.96-4.44)	0.062
NYHA class I-II vs. III-IV	-0.177	<.001	0.040	0.506	0.95 (0.46-1.96)	0.883
Hypertension	0.032	0.490	-0.049	0.415	0.50 (0.28-0.89)	0.019
Previous heart failure	-0.141	0.002	-0.012	0.847	1.25 (0.62-2.51)	0.528
Atrial fibrillation	-0.081	0.083	0.115	0.053	1.96 (0.90-4.24)	0.089
Diabetes	0.020	0.664	0.025	0.672	0.49 (0.21-1.13)	0.094
Previous stroke	-0.149	0.001	0.036	0.549	1.01 (0.41-2.51)	0.982
Heart rate	-0.127	0.006	-0.107	0.071	0.87 (0.58-1.14)	0.237
Haemoglobin	0.125	0.007	-0.071	0.234	0.77 (0.60-1.13)	0.137
Creatinine clearance	0.182	<.001	-0.075	0.207	0.73 (0.53-1.00)	0.071
Cholesterol	0.067	0.151	0.070	0.242	1.13 (0.84-1.52)	0.411
LDL cholesterol	0.02	0.664	0.082	0.171	1.16 (0.87-1.54)	0.322
HDL cholesterol	0.174	<.001	-0.015	0.802	0.96 (0.72-1.29)	0.798
Triglycerides	-0.079	0.091	0.036	0.551	1.06 (0.78-1.44)	0.710
BNP	-0.151	0.001	0.140	0.019	1.55 (1.13-2.12)	0.007
Systolic BP	0.060	0.197	-0.056	0.348	1.00 (0.61-1.27)	0.499
Diastolic BP	0.085	0.070	-0.062	0.297	0.80 (0.58-1.00)	0.071
Baseline MMSE	-	-	0.007	0.906	0.34 (0.23-0.89)	<.001

*Table 7***.** Multivariable logistic regression model presenting adjusted odds ratios (OR) and 95% confidence intervals (CI) per 1 standard deviation increase in clinical variables for the association with future dementia. The model on the left includes the variables significant in Table 6. The model on the right is similar but also adjusted with the baseline MMSE.

	OR (95% CI)	**p-value**	**MMSE adjusted OR (95% CI)**	**p-value**
Age	1.30 (0.89-1.88)	0.172	1.28 (0.73-1.60)	0.18
Hypertension	0.53 (0.27-0.95)	0.034	0.52 (0.27-1.00)	0.05
Education in years	0.50 (0.33-0.77)	0.001	0.69 (0.44-1.07)	0.10
BNP	1.53 (1.09-2.16)	0.016	1.46 (1.03-2.09)	0.03

Testing was further extended to subgroups of participants with no previously diagnosed heart failure (n=346) and no stroke history (n=413). In a subgroup with no previous heart failure, BNP was significantly associated with new dementia cases when tested both alone (HR=1.49; 95% CI, 1.07-2.09; p=.020) and in a multivariable model with age, the duration of education and diagnosed hypertension (HR=1.51, 95% CI, 1.05-2.18; p=.026). In a subgroup free of stroke, BNP remained a significant predictor of future dementia with no material change in the results (data not shown).

Dementias were further classified as AD (n=42), Vad (n=10), dementia with Lewy bodies (n=3) and other dementias (n=4). The BNP levels of the participants with no dementia, AD and VaD at follow-up are presented using a box-plot in Figure 3. When studied separately according to the type of dementia, baseline BNP was predictive of both AD (HR, 1.59; 95% CI, 1.09-2.30; p= .015) and VaD (HR, 2.71; 95% CI, 1.31-5.60; p= .007)

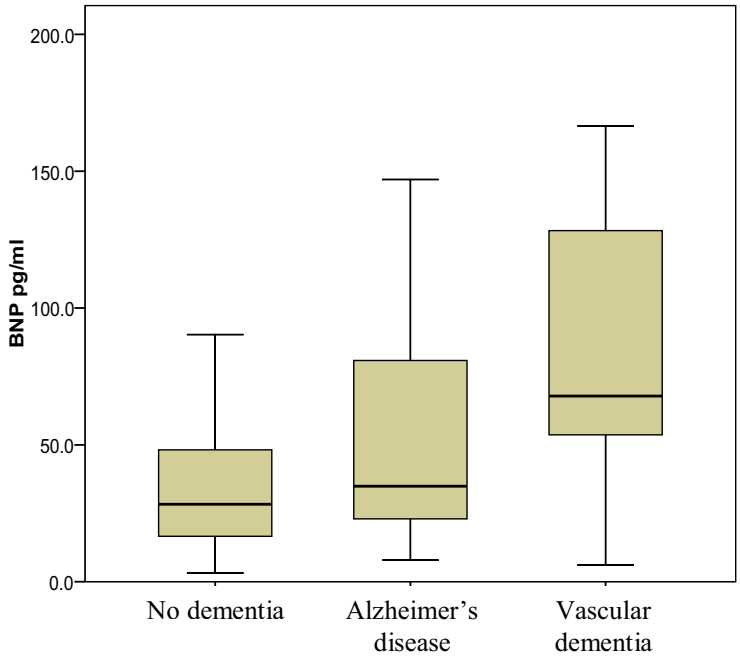


Figure 3. Mean±standard deviation B-type natriuretic peptide (BNP) of the participants. Participants divided into groups according to their follow-up visit dementia status. Participants with no dementia (N=230) BNP=39.3±37.2 pg/ml, Alzheimer's disease (N=42) BNP=56.9±57.6 pg/ml, Vascular dementia (N=10) BNP=79.6±56.7 pg/ml. ANOVA p= .001 in between the groups (Study III).

5.4 B-TYPE NATRIURETIC PEPTIDE AND MINI MENTAL STATE EXAMINATION SCORE AS PREDICTORS OF MORTALITY

Predicting the power of clinical variables on total and cardiovascular mortality with the special emphasis on BNP and MMSE score was studied in a subgroup of the participants as described in detail in **4.8.4**. Participants were divided according to their survival status for the analysis of baseline characteristics. During a median follow-up period of 8.4 years (8.2–8.6) for survivors and 7.9 years (2.7–8.4) for the whole study population, 258 (51.7%) participants expired, producing an annual mortality rate of 8.3%. The cause of death was cardiovascular in 139 (53.9%) cases – malignancy with 44 (17.1%) and infection with 22 (8.5%) deaths being the other common causes.

Compared with survivors, the non-survivors were older and more likely to have a history of heart failure, atrial fibrillation, or stroke. (Table 8). In a comparison, BNP was 48.6 pmol/L (24.0–86.5) for non-survivors vs. 27.2 pmol/L (16.2–47.9) for survivors ($p< .001$). The MMSE score among the non-survivors was 26 (24–29) and among survivors 28 (25–29) ($p< .001$).

5.4.1 Predictors of total mortality

MMSE score and BNP as continuous and dichotomous variables were significantly linked to mortality when tested alone or in a sex and age-adjusted model. The age- and sex-adjusted mortality risk increased with the increase in the quintile of BNP and MMSE score. The HR between the lowest and highest quintile for BNP was 2.75, and for MMSE the HR was 2.01. Sex and age-adjusted survival curves and their significance are presented in Figure 4.

In a fully adjusted multivariable model with multiple predefined clinical correlates as co-variables, BNP was a clear and MMSE score a borderline prognostic predictor of mortality. The HRs and their significance are presented in Table 9. Concerning other significant predictors in the model, age (HR=1.71; 95% confidence interval [CI]=1.42–2.11; $p< .001$), systolic blood pressure (HR=0.80; 95% CI=0.68–0.98; $p= .029$), diabetes (HR=1.65; 95% CI=1.14–2.38; $p= .008$), continuous MMSE score (HR= 0.81; 95% CI=0.70–0.94; $p= .007$), and continuous BNP (HR=1.44; 95% CI=1.22–1.77; $p< .001$) were independently associated with mortality. Regarding cardiovascular morbidities, only a history of stroke showed a trend towards greater mortality (HR=1.53; 95% CI=0.98–2.36, p=.07). A history of heart failure, myocardial infarction or atrial fibrillation was not independently associated with total mortality ($p> .100$ for all).

5.4.2 Predictors of cardiovascular mortality

MMSE score and BNP as continuous and dichotomous variables were significantly linked to mortality when tested alone or in a sex- and age-adjusted model. The age- and sex-adjusted mortality risk increased significantly with the increase in the quintile of BNP. HR between the lowest and highest quintile for BNP was 3.29. A similar model for the MMSE score showed only a trend towards higher mortality among the participants with the higher MMSE score (HR 1.49). Age- and sex-adjusted survival curves and their significance are presented in Figure 4.

Table 8. Baseline characteristics of the participants with an MMSE >17 points by their survival status (Study IV)

	Survivors (n=258)	**Nonsurvivors (n=241)**	**p-value**
Age in years , mean (SD)	78.5 (3.4)	81.4 (4.5)	<.001
Women, n (%)	182 (75.2)	179 (69.4)	0.126
BMI, mean (SD)	27 (4.2)	25.8 (4.7)	0.005
Smoking, n (%)	57 (23.7)	73 (28.4)	0.227
NYHA class III or IV (%)	45 (19)	73 (30.7)	0.003
MMSE score, median (IQR)	28 (25-29)	25 (23-28)	<.001
MMSE score <24 points, n (%)	31 (12.9)	85 (32.9)	<.001
Dementia at examination, n (%)	8 (3.3)	37 (14.3)	<.001
Education in years, mean (SD)	6.9 (3.4)	6.8 (3.5)	0.798
Zung's self-rating depression scale, mean (SD)	38.2 (7.7)	40.7 (8.0)	0.001
Medication			
Regular medication, n (%)	209 (86.7)	239 (92.6)	0.029
Beta-blocker, n (%)	105 (43.6)	113 (43.8)	0.959
ACE-i/ARB, n (%)	45 (18.7)	57 (22.1)	0.344
Diuretics, n (%)	65 (27.0)	112 (43.4)	<.001
Ca-channel blockers, n (%)	42 (17.4)	44 (17.1)	0.912
Statins, n (%)	20 (8.3)	3.0 (1.2)	<.001
Previous illnesses			
Previous MI, n (%)	70 (29.0)	95 (36.8)	0.065
Hypertension, n (%)	157 (65.1)	143 (55.4)	0.084
Heart failure, n (%)	39 (16.2)	84 (28.6)	<.001
Atrial fibrillation, n (%)	28 (11.6)	48 (18.6)	0.03
Diabetes, n (%)	41 (17.0)	62 (24.0)	0.053
Previous stroke, n (%)	11 (4.6)	38 (14.7)	.<001
Heart rate per minute, mean (SD)	68.4 (13.7)	68.7 (13.2)	0.834
Systolic BP, mean (SD), mmHg	157.2 (23.7)	147.7 (23.9)	<.001
Diastolic BP, mean (SD), mmHg	78.2 (10.0	74.7 (11.4)	<.001
Laboratory data			
Haemoglobin, mean (SD), g/l	134.9 (11.7)	131.8 (13.6)	0.006
BNP, median (IQR), pmol/L	27.3 (16.2-47.9)	48.6 (24.0-86.5)	<.001
Creatinine clearance, mean (SD), ml/min	55.3 (14.7)	49.4 (15.6)	<.001
fP-glucose, mean (SD), mmol/l	5.5 (1.2)	5.7 (1.4)	0.352
Lipids			
Cholesterol, mean (SD), mmol/l	5.9 (1.08)	5.5 (1.17)	0.001
LDL cholesterol, mean (SD), mmol/l	4.0 (0.98)	3.8 (1.12)	0.0019
HDL cholesterol, mean (SD) mmol/l	1.55 (0.40)	1.40 (0.41)	<.001
Triglycerides, median (IQR), mmol/l	1.32 (0.95-1.30)	1.32 (0.97-1.78)	0.738

The independent predictors of cardiovascular mortality in a multivariable Cox model were age (HR=1.71; 95% CI=1.42–2.75; p< .001), systolic blood pressure (HR=0.74; 95% CI=0.58–0.95; p= .016), NYHA class III–IV vs. I–II (HR=1.64; 95% CI=1.02–2.64; p= .044), diabetes (HR=1.71; 95% CI= 1.05–2.80; p= .033), and BNP (HR= 1.72; 95% CI=1.37–2.15; p< .001). None of the cardiovascular conditions with an association to mortality (P< .100) were independent predictors of cardiovascular mortality when tested in the multivariable model (P>.100 for all).

Importantly, the MMSE score showed no association with cardiovascular mortality either as a continuous variable or in a dichotomous formulation when the known risk-factors were fitted into the same model (Table 9). Removing BNP from the model did not materially change the result for MMSE score.

Table 9. Hazard ratios (HR) for total and cardiovascular mortality during a median mollow-up of 7.9 years according to baseline BNP and MMSE score (Study IV)

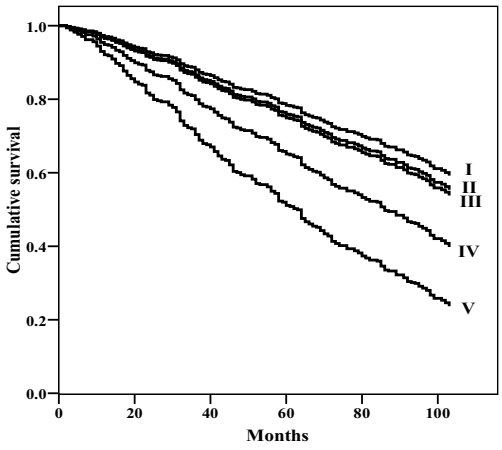
Total mortality	**HR (95% CI) per 1-SD increase in log variable**	**p-value**	**HR (95% CI) for values above the 80th percentile for †BNP and below the 20th percentile for ‡MMSE score**	**p-value**
BNP				
Unadjusted model	1.64 (1.44-1.87)	<.001	2.63 (2.00-3.44)	<.001
Age- and sex-adjusted model	1.47 (1.30-4.06)	<.001	2.17 (1.65-2.86)	<.001
Multivariable model #	1.44 (1.22-1.70)	<.001	1.85 (1.28-2.66)	0.001
MMSE score				
Unadjusted model	0.65 (0.58-0.73)	<.001	2.32 (1.79-3.01)	<.001
Age- and sex-adjusted model	0.74 (0.65-0.84)	<.001	1.82 (1.38-2.41)	<.001
Multivariable model #	0.81 (0.70-0.94)	0.007	1.40 (1.00-1.97)	0.048
Cardiovascular mortality				
BNP				
Unadjusted model	1.84 (1.56-2.18)	<.001	3.01 (2.11-4.29)	<.001
Age- and sex-adjusted model	1.65 (1.38-1.97)	<.001	2.40 (1.65-3.43)	<.001
Multivariable model #	1.72 (1.37-2.15)	<.001	2.18 (1.32-3.56)	0.002
MMSE score				
Unadjusted model	0.68 (0.58-0.79)	<.001	2.21 (1.55-3.17)	<.001
Age- and sex-adjusted model	0.81 (0.68-0.96)	0.017	1.62 (1.1-2.38)	0.013
Multivariable model #	0.92 (0.75-1.14)	0.437	1.11 (0.70-1.76)	0.659

†Hazard ratio for participants with values above the 80th percentile relative to the rest of the participants, the 80th percentile corresponding to values 79.7pg/mL or more for BNP.

‡Hazard ratio for participants with values below the 20th percentile relative to the rest of the participants, the 20th percentile corresponding to values less than 24 poits in MMSE score.

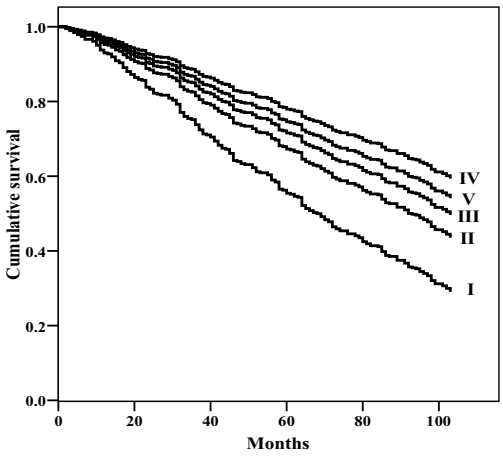
All parameters with p<100 in Table 1 were included in the multivariable model. Because of mutual dependency, only one of the lipid parameters, HDL cholesterol, was included. Similarly, only systolic blood pressure was included. Adjustment for age, body mass index, New York Heart Association class I-II or III-IV, heart failure, systolic blood pressure, hypertension, previous myocardial infarction, atrial fibrillation, stroke, diabetes, haemoglobin, high density lipoprotein, creatinine clearance, as well as adjustment for MMSE in analysis for BNP and adjustment for BNP in analysis for MMSE.

A.



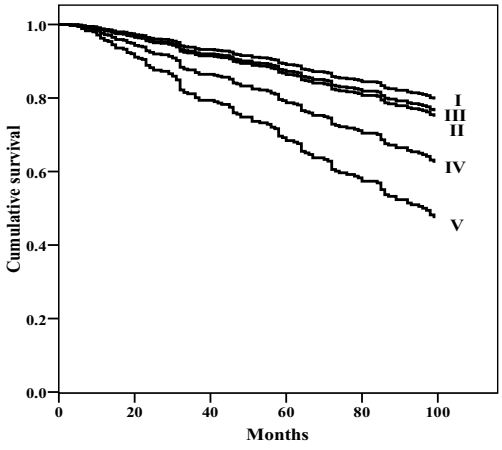
No at risk						
I	99	93	90	80	74	34
II	99	95	84	74	68	33
III	98	91	79	71	60	26
IV	101	88	76	63	52	24
V	97	74	54	42	30	12

B.



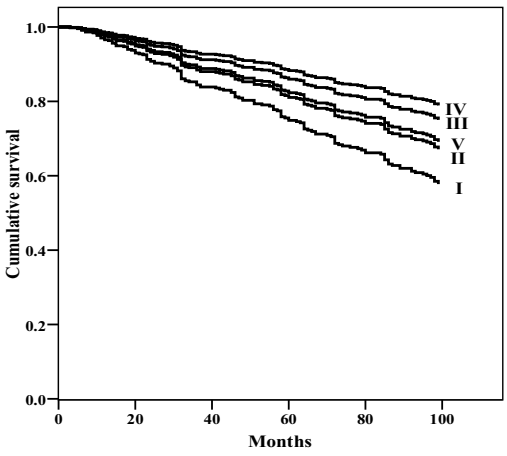
No at risk						
I	116	96	74	50	39	15
II	88	77	67	57	43	18
III	92	83	71	63	57	26
IV	72	67	61	57	53	27
V	132	123	115	106	91	43

C.



No at risk						
I	99	93	90	80	74	34
II	99	95	84	74	67	33
III	98	91	79	71	60	26
IV	101	88	76	63	52	24
V	97	74	55	42	30	12

D.



No at risk						
I	116	97	74	50	39	15
II	88	78	67	57	43	18
III	92	83	71	63	57	26
IV	72	67	61	57	55	27
V	132	123	115	106	91	43

Figure 4. Age- and sex-adjusted Cox proportional hazards survival curves for total and cardiovascular mortality divided by B-type natriuretic peptide (BNP) and Mini Mental State Examination Test (MMSE) quintiles (I-V), separately, in the entire study population (n=499). (A) BNP and total mortality (*P* for trend < .001); (B) MMSE and total mortality (*P* < .001); (C) BNP and cardiovascular mortality (*P* < .001); (D) MMSE and cardiovascular mortality (*P*= .067). The BNP quintiles were 3.2–17.0, 17.2–28.0, 28.2–45.3, 46.2–78.8 and 79.7–500 pg/mL. The MMSE score quintiles were 18 to 23, 24 to 25, 26 to 27, 28 and 29 to 30 (Study IV)

6 Discussion

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Risk markers for cardiovascular disease and cognitive dysfunction

Risk assessment is essential in clinical decision-making when directing resources, weighing alternative management strategies and choosing the best course of treatment for a patient. In the context of cardiovascular disease, risk stratification for the general population can lead to, for example, better allocation of the limited coronary angiography or echocardiography resources, or a more effective use of primary preventive medications or other preventive interventions, such as smoking cessation, at the population level (Hlatky et al. 2009).

A prospective cohort study is the best tool for estimating the power of a certain risk marker in predicting the defined end-point in the population (von Elm et al. 2007). The risk of a certain outcome over the follow-up is then measured and reported by using a survival curve or reporting the number of events over the given time period. The statistical association of the risk-marker with a predefined end-point can be studied by using logistic regression or the Cox proportional hazards model. (Harrell et al. 1996) Logistic regression is preferred when the follow-up time is fixed and short, as was the case in our analysis regarding the prognostic value of BNP concerning the occurrence of dementia during the fixed follow-up period of five years. The Cox proportional hazards model is more suitable when the follow-up period varies or is longer, as was the case in our analysis of the effect of BNP and MMSE on mortality. (Harrell et al. 1996) Several critical issues have to be considered when these statistical methods are used. Firstly, it is essential that the number of outcome events over the follow-up period is sufficient. The number of the events, not the size of the study population, is crucial when the significance of a certain risk-marker is estimated. (Hlatky et al. 2009) In the present study, the main outcome measures were mortality and newly diagnosed dementias during the follow-up. The number of patients who expired was 258 out of the 499 individuals in Study IV and 177 out of the 355 individuals in Study II, producing outcome numbers comparable or superior to the events in similar types of studies with considerably larger populations (Kelman et al. 1994; Bella et al. 2002; Redfield et al. 2003; Kistorp et al. 2005; Strandberg et al. 2009).

Secondly, the risk marker should offer information beyond the basic demographic parameters and established risk markers (Hlatky et al. 2009). In the context of cardiovascular disease, this means that any novel prognostic marker should improve the prediction in addition to the individual's age, sex, smoking status, blood pressure, lipid levels and the possible presence of diabetes (Wilson et al. 1998; Roques et al. 2003). A greater number of outcomes is necessary when testing the prognostic power of the risk marker together with previously defined risk markers compared to univariable analysis (Harrell et al. 1996). We used the above-mentioned covariates routinely in the analysis included in our study.

6.1.2 Study population

This thesis is based on the analysis of a well-defined, stratified population-based cohort of elderly people in the area of Kuopio, eastern Finland, in 1998. The refusal rate was only 14%, which is very low when compared to other studies with a similar kind of approach.

(Bassuk et al. 2000; Nguyen et al. 2003; Kistorp et al. 2005; Kardys et al. 2009) The generalisability of the results among the Finnish elderly population is therefore presumably good. The study was carried out in an almost exclusively white Caucasian population, which limits the use of the results for other ethnic groups.

The present data was collected in 1998, thirteen years ago; the use of cardiovascular medication among the elderly has changed since then (Hiitola et al. 2007) and the invasive treatment of cardiovascular disease is more active today in comparison to the period of the data collection (Scarborough et al. 2010). This type of limitation is inherent to all long-term follow-up studies due to the continuous evolvement of medical treatment.

6.1.3 Study design

The purpose of the Kuopio 75+ study was originally to examine the clinical epidemiology of diseases, especially those causing dementia. Therefore, the analyses of cardiovascular morbidity and mortality have to be considered secondary in nature. In our study population, the prevalence of heart failure (24.6%) and other cardiovascular conditions was markedly greater than in most of the studies focused on the epidemiology of heart failure (Kupari et al. 1997; Redfield et al. 2003). The diagnosis of heart failure was obtained from medical records, which may have caused a degree of over-diagnosis. Nevertheless, Eastern Finland is known for an exceptionally high cardiovascular disease burden (Pyörälä et al. 1985).

Echocardiographies were carried out in random fashion by a single experienced cardiologist (prof. Raimo Kettunen) unaware of other study results. The tissue Doppler method allowing accurate measurement of diastolic dysfunction was not available at the time. It would have been of interest to see the dependence of diastolic dysfunction on HDL cholesterol and BNP, and its association with mortality, in this cohort of elderly subjects. One strength of the study was that the diagnosis and classification of dementing illnesses were made by an experienced neurogeriatrician (prof. Raimo Sulkava), and brain imaging by means of CT or MRI was routinely used.

6.2 HIGH-DENSITY LIPOPROTEIN AND SYSTOLIC DYSFUNCTION

HDL cholesterol was found to be significantly associated with systolic function of the heart, while BNP showed no connection to echocardiographically measured ejection fraction. The mechanism linking HDL cholesterol to systolic function is not clear. More extensive coronary disease, caused by low HDL cholesterol, leading to cardiac ischemia could serve as an explanation. Notably, the use of long-acting nitrates, a previous myocardial infarction, and the presence of arteriosclerosis obliterans (ASO) or diabetes were not significantly linked to systolic function. This could implicate that a mechanism independent of coronary disease could partly explain the connection between HDL cholesterol and systolic function.

Traditionally, HDL is known for its ability to remove excessive cholesterol from its target organ, mostly the vascular system, and therefore to have an atheroprotective effect. Apart from its cholesterol transport function, HDL has potent anti-inflammatory and oxidation-preventing properties (Banka 1996; Sviridov et al. 2008). HDL also has an anti-thrombotic and anti-adhesive effect on platelets and is known to protect endothelial function by stimulating endothelial nitric oxide synthase (Sviridov et al. 2008). Oxidative stress and endothelial dysfunction have been connected to heart failure and could partly

explain the association between systolic function and HDL cholesterol (Bergamini et al. 2009).

There is accumulating evidence that the plasma concentration of HDL cholesterol is not the only determinant of its atheroprotective capacity (Sviridov et al. 2008). The HDL functionality, mostly independent of its concentration, is as important in determining the atherogenic capacity of HDL. HDL contains many other lipids and proteins in addition to cholesterol, and measuring the plasma HDL cholesterol concentration does not take into account possible functional differences in HDL particles and therefore possibly underestimates the true effect of HDL on systolic function (Vaisar et al. 2007).

Low total cholesterol is known to correlate with excess mortality in the elderly population (Weverling-Rijnsburger et al. 1997). Additional mortality has been mainly due to infectious diseases and neoplasms (Weverling-Rijnsburger et al. 1997). Cardiovascular mortality has not been affected, implicating that low HDL cholesterol and its correlation with systolic dysfunction is likely to be a separate issue from the previously-mentioned one. In heart failure patients, low cholesterol also correlates with excess mortality (Rauchhaus et al. 2003). Statin therapy has been associated with lower mortality – regardless of lipid levels and the presence or absence of coronary disease in a large epidemiological study (Go et al. 2006). The anti-inflammatory and anti-oxidative effects of statins have been suggested to be the mechanisms of positive statin effect on cardiac function (Sola et al. 2006). On the other hand, in two prospective randomised trials studying the prognostic effect of rosuvastatin therapy on heart failure patients with systolic dysfunction (Kjekshus et al. 2007) and patients with systolic or symptomatic diastolic dysfunction (Tavazzi et al. 2008), no mortality benefit was seen.

6.3 B-TYPE NATRIURETIC PEPTIDE AND SYSTOLIC DYSFUNCTION

As expected, BNP levels were significantly higher, and a history of diabetes, significant valvular disease, ASO and myocardial infarction more common among participants with previously diagnosed heart failure, when compared with the rest of the study population. In contrast, systolic dysfunction, measured by EF, was not significantly linked to BNP or any other of these variables. In an earlier study, with a similar type of setting conducted on elderly individuals, BNP was found to associate with systolic dysfunction (Smith et al. 2000). Compared with the study mentioned, our study population was larger, the recruiting of the intended cohort more successful, and the cardiovascular conditions and medication were reported. It is possible that differences in these factors explain the contradictory findings. It has been proposed that natriuretic peptides, BNP and NT-BNP could be used as a screening test for cardiac systolic dysfunction in high-prevalence populations, including the elderly (Alehagen et al. 2003; Heidenreich et al. 2004). The prevalence of systolic dysfunction (defined as EF 45% or lower) in our general population was 24% and, based on earlier data, it could have been expected that BNP would have performed better in recognising patients with reduced EF. Significant valvular disease was associated with BNP in our study population, whereas HDL cholesterol did not show any association. Symptomatic heart failure in the elderly is predominantly caused by diastolic dysfunction (Kupari et al. 1997) which, together with valvular disease, is likely the main explanation for the poor link between BNP and systolic dysfunction. Furthermore, diuretics and drugs influencing the RAA have a well-established moderating influence on

blood BNP (Vuolteenaho et al. 2005), and their use may partly explain the lack of association between BNP and ejection fraction.

6.4 INVERTED MITRAL INFLOW PATTERN AND TOTAL, CARDIOVASCULAR AND NON-CARDIOVASCULAR MORTALITY

Inverted mitral inflow, defined as an E/A ratio of less than 0.75, was the strongest predictor of mortality out of the measured echocardiographical parameters. Interestingly, the prognostic value of an inverted mitral inflow pattern was mainly driven by its association with non-cardiovascular mortality, with no significant connection to cardiovascular mortality. Earlier studies on the prognostic value of inverted mitral inflow pattern have been unanimous in their message: inverted mitral inflow has been a strong predictor of mortality (Bella et al. 2002; Redfield et al. 2003; Kardys et al. 2009). The studies have been carried out with younger populations with lower mortality rates. The only study to report on total and cardiovascular mortality separately connected inverted E/A with both end-points, but, interestingly, the connection to cardiovascular mortality was not independent of covariates (Bella et al. 2002). It would be of great interest to revisit the data of larger population-based studies to ascertain the possible connection of inverted mitral inflow with non-cardiovascular mortality.

It would have been necessary to include either pulmonary vein inflow Doppler measures or tissue Doppler measures to differentiate the truly normal mitral inflow from a pseudonormal pattern, which is a sign of impaired ventricular relaxation with elevated filling pressures. Therefore, participants with a "normal" mitral inflow pattern, E/A 0.75–1.5, in this elderly general population with a high prevalence of cardiovascular disease have to be considered to have indeterminate diastolic function. To the contrary, those with E/A less than 0.75 have clearly abnormal diastolic function based on validated classifications (Ommen et al. 2000; Oh et al. 2006). A high prevalence of participants with a pseudonormal pattern could explain the higher levels of BNP among participants with E/A 0.75–1.5. Furthermore, the use of diuretics, known for their lowering effect on BNP (Vuolteenaho et al. 2005), was more common among participants with E/A < 0.75, but it did not seem to explain the prognostic power of inverted mitral inflow in the multivariable model (Table 2). The higher total mortality among participants with an inverted mitral inflow pattern but lower BNP levels, and the higher incidence of non-cardiovascular causes of death during the follow-up, is somewhat unexpected and serves as a ground for speculation backed up by other findings in the population.

Among populations of advanced age, the attenuation of the E/A ratio can be caused by many mechanisms not related to heart failure (Finucci et al. 1996; Bossone et al. 1999; Salerno et al. 2003; Gurudevan et al. 2007). The elderly often have an impaired ability to sense thirst (Waldreus et al. 2010), and chronic dehydration is common among the elderly, especially among cognitively impaired individuals (Morley 2002). Dehydration is known to co-exist with malignancies (Price 2010). It decreases the filling pressure of the left ventricle, which attenuates the E wave and, consequently, lowers the mitral E/A ratio. Cognitive impairment and, in particular, dementive illnesses are known to have a remarkable impact on prognosis (Kelman et al. 1994; Larson et al. 2004). In our study population, various forms of dementia were significantly more common among participants with an inverted mitral inflow pattern. Cholesterol metabolism has been linked to cognitive decline in multiple studies (Kerola et al. 2011), and a recent analysis

carried out among the HYVET study population connected a low level of HDL cholesterol to a faster cognitive decline in a hypertensive elderly population (Peters et al. 2009). The HDL cholesterol level was also significantly lower in our study among participants with an E/A < 0.75. An inverted mitral inflow pattern is known to be more common among individuals with chronic lung disease or chronic pulmonary embolism (Bossone et al. 1999; Gurudevan et al. 2007) – in our population, there was a trend towards more astma/COPD cases among participants with an E/A ratio of under 0.75. Liver failure is also known to cause intravascular hypovolaemia, and an inverted mitral inflow pattern has been shown to co-exist with liver cirrhosis (Finucci et al. 1996; Salerno et al. 2003). Unfortunately, liver function was not measured in the present data.

These non-cardiovascular conditions could possibly explain the association of inverted mitral inflow with excess non-cardiovascular mortality. In concordance with this reasoning, one earlier study among the elderly using pulsed Doppler measures of pulmonary venous flow for differentiating a pseudonormal from a normal mitral inflow found that N-terminal ProBNP levels were lower among participants with an inverted mitral inflow pattern when compared to counterparts with diastolic function classified as normal based on mitral inflow (Alehagen et al. 2003). Importantly, E/A can be recorded only when sinus rhythm is present, and participants with atrial fibrillation were excluded from these analyses.

6.5 LEFT VENTRICULAR MASS, EJECTION FRACTION AND MORTALITY

The left ventricular mass index was a significant predictor of total mortality in the models applied. This finding is in the line with several earlier larger population-based studies in populations with varying age compositions (Levy et al. 1990; Gardin et al. 2001; Kardys et al. 2009). As expected, the predicting power of left ventricular mass was due to its association with cardiovascular mortality, whereas it showed no connection to non-cardiovascular mortality.

Ejection fraction as a continuous parameter showed no association with mortality in our study. This finding is most probably due to a lack of power, since previous larger population-based studies have found EF to predict both total and cardiovascular mortality (Aurigemma et al. 2001; Devereux et al. 2003; Redfield et al. 2003; Wang et al. 2003), with a single exception (Kardys et al. 2009). Importantly, our study population demonstrated a trend towards higher mortality among participants with severely reduced ejection fraction (<35%).

6.6 BNP AND COGNITIVE DYSFUNCTION

We found BNP to be associated with all the measured cognitive endpoints: baseline MMSE, the decline oinf the MMSE during the follow-up and, most importantly, new diagnoses of dementing illnesses during the follow-up. Several previously known risk markers for cognitive impairment, such as low educational level, age as well as cardiovascular illnesses and risk markers, were associated with baseline MMSE, but none of these were linked to the further decline in MMSE over the follow-up in this elderly population free of dementia at baseline; remarkably, BNP was the only variable to be

connected with this outcome. The association between the decline in MMSE and BNP was not explained by the commonly known confounding factors of age, sex, total years of education, depression or baseline MMSE.

The prevalence of dementia at baseline in the present study population was 22.8%, being in concordance with previous data (Evans et al. 1989). Similarly, the high annual mortality rate of 8.1% during the follow-up was expected in this elderly population. A high level of natriuretic peptides and dementia are both known to associate with excess mortality in the elderly (Jagger et al. 2000; Kistorp et al. 2005). The use of diuretics and agents affecting the renin-angiotensin system, known also to lower the level of BNP, was more common among participants with a higher level of BNP in the present study. Hence, high mortality and the use of medication affecting the BNP level might even have attenuated the ability of BNP to predict cognitive decline.

HDL (but not total) cholesterol was associated with a low MMSE score at baseline, but it did not predict further decline in cognitive function in our study. This is in concordance with earlier reports where lipid levels in middle-age, but not in later years, were associated with future cognitive impairment (Notkola et al. 1998; Kloppenborg et al. 2008). The existing literature supports the notion that the relation between blood pressure and cognitive level is age-dependent. In studies conducted on middle-aged populations, hypertension has predicted cognitive impairment (Launer et al. 2000; Kivipelto et al. 2005), but the role of blood pressure in cognitive decline in the elderly is less clear: some studies have (Yoshitake et al. 1995) but most have not (Posner et al. 2002; Kloppenborg et al. 2008) reported an association between blood pressures and cognitive decline. On the contrary, in late-life cross-sectional studies low blood pressure has been constantly associated with poor cognitive function (Guo et al. 1996; Kloppenborg et al. 2008). In our study, there was a trend towards an association between low diastolic pressure and new onset of dementias. Interestingly, a diagnosis of hypertension was associated with a lower incidence of dementia in the follow-up, independently of previously known risk factors of dementia. This may be explained by the more common use of antihypertensive medication among participants who have been diagnosed with hypertension (P<.001 for all classes of antihypertensive medication, separately, data not shown). This is backed up by earlier epidemiological studies in which the use of antihypertensive medication has been associated with a lower incidence of cognitive decline (Guo et al. 1999; Veld et al. 2001; Li et al. 2010). The analysis from the extensive database of 819,491 predominantly male individuals indicated that ACE inhibitors offer additional benefit when compared to other antihypertensive drugs in terms cognitive measures (Li et al.). An analysis from the Cardiovascular Health Study indicated that the use of ACE inhibitors crossing the blood brain barrier might be associated with better outcome in terms of cognitive function (Sink et al. 2009). In our study population, 59 participants used ACE inhibitors, and there was a trend towards a lower frequency of diagnosed dementia among ACE inhibitor users (OR=0.476; p=0.100). The data is too limited for further analysis between different types of ACE inhibitors.

So far, randomised placebo-controlled studies with antihypertensive medications have included cognitive measures as a secondary end-point, and the results have been conflicting (Applegate et al. 1994; Forette et al. 1998; Skoog et al. 2005; Peters et al. 2008; Anderson et al. 2011)

Blood pressure amongst the aged may not be as good a marker of cardiovascular morbidity as in younger populations, since it is attenuated by many factors common in the elderly population, such as dehydration, heart failure, atrial fibrillation and aortic stenosis. Therefore, it is possible that the heart and cardiovascular system are under stress and predispose to cognitive impairment even if blood pressure is not elevated. It is also

possible that elevated blood pressure in the elderly is an indicator of robust cardiac pump function, which in turn is required for adequate perfusion through an aged vasculature to various organ systems, including the brain.

BNP is a marker of cardiac – especially left ventricular – pump function and has been linked to both cardiovascular and total mortality in the general elderly population (Kistorp et al. 2005). In heart failure patients, high levels of BNP have been linked to cognitive dysfunction in a small (n=60) cross-sectional trial. Heart failure, linked to BNP, did not predict cognitive decline or dementia in the present data. The explanation for the ability of BNP to predict forthcoming cognitive impairment is not clear. In our study, the history of stroke was taken into account, and it did not predict cognitive decline as BNP did (Table 2). The predictive value of BNP was further tested in subgroup analyses in participants with no history of heart failure or stroke, separately, with no material change in results. High levels of BNP are associated with endothelial dysfunction, and this phenomenon has recently been linked to cognitive function (Chong et al. 2004).

As expected, the majority of the participants with dementia in our study population were diagnosed with Alzheimer's disease. BNP was associated with multiple baseline parameters, such as age and low BMI, previously found to be associated with Alzheimer's disease. MR-proANP is a stable form of the N-terminal fragment of proatrial natriuretic peptide. In line with the studies on the association of MR-proANP with the presence of dementia and the predictive value for future dementia by Buerger et al. (Buerger et al. 2009; Buerger et al. 2011), BNP, a potent vasodilatator, was significantly associated with both new cases of Alzheimer's disease and vascular dementia in a subgroup analysis. The association with vascular dementia appeared to be even stronger than with Alzheimer's disease, but the results with a small number of vascular dementia cases (N=10) should be interpreted with caution.

Despite the contradictory results in the elderly regarding the association between hypertension and dementia, it is important to remember that treatment of hypertension has been highly efficacious also among elderly patients in preventing mortality and cardiovascular events. Therefore, enough evidence exists to guide pharmacological treatment in older patients for hypertension and dyslipidaemia, even though the evidence is not sufficient in terms of dementia prevention. Aggressive reduction of blood pressure should be avoided in the very old, given the unwarranted negative cognitive consequences.

6.7 B-TYPE NATRIURETIC PEPTIDE AS A PREDICTOR OF MORTALITY IN THE ELDERLY

BNP was a powerful, independent predictor of total and cardiovascular mortality, as expected based on the results on earlier studies addressing the issue (Wallen et al. 1997; Kistorp et al. 2005). Several recent studies have suggested that cardiovascular morbidity and cognitive dysfunction are closely connected among the elderly (Morris et al. 2001; Iadecola et al. 2008; Kloppenborg et al. 2008; Buerger et al. 2011). In the present study – even after adjusting for cognitive function measured by the MMSE score – BNP remained a robust predictor of total and cardiovascular mortality. Considering the known association with heart failure, BNP was also studied in the subgroup of participants who had no previously diagnosed heart failure, with no material changes in the results.

Altered levels of BNP are known to be associated with several cardiovascular conditions, such as hypertension, atrial fibrillation, history of myocardial infarction and, particularly, heart failure caused by systolic or diastolic cardiac dysfunction (Vuolteenaho et al. 2005). Diastolic heart failure and asymptomatic cardiac dysfunction are exceedingly common among the aged (Redfield et al. 2003), and they are likely to explain some of the good predictive value of BNP on mortality in an elderly population. We used clinical manifestations of the above-mentioned diseases as covariates in our multivariable analysis, but BNP consistently remained a significant variable in the models. Furthermore, the median BNP level in our study was remarkably low as compared to patients with clinical heart failure. These findings underscore the predictive importance of even modest increases in BNP.

Traditional cardiovascular risk markers such as hypertension, dyslipidaemia, and obesity are known to lose much if not all of their prognostic power when measured in the elderly (Oates et al. 2007; Takata et al. 2007). *Low* blood pressure and *low* cholesterol have often served as predictors of mortality when studied among the aged population. Both of these parameters also had the inverse association with mortality in our study, even though low total cholesterol only in a univariable model. Systemic blood pressure is attenuated by several conditions frequently found in the elderly population, such as heart failure, atrial fibrillation, aortic stenosis and dehydration. All of these derangements are associated with increased mortality, deteriorating the prognostic value of hypertension among elderly. Thus, it is possible that the heart and cardiovascular system is under stress – as evident in the relative increase in the BNP level – even in the case of normal or even low blood pressure. This is also a putative mechanism for antihypertensive medication, which is protective against dementia even in the presence of normal blood pressures.

A history of atrial fibrillation, symptomatic heart failure, myocardial infarction or stroke were more common among the individuals who expired; only a history of stroke had any connection with mortality in the multivariable models. In line with previous studies, a high NYHA class and diabetes were associated with cardiovascular mortality. This corresponds with earlier mortality studies conducted in the elderly: the quantitative characteristics of disease severity, such as NYHA class, BNP or the MMSE score, are stronger determinants of prognostic impact than the sheer existence of the condition (Fried et al. 1998). CRP, a marker of inflammation and an extensively studied cardiovascular risk marker, has also performed worse in prognostic studies conducted in the elderly (Strandberg et al. 2000; Kistorp et al. 2005), while BNP as a direct marker of left ventricular stretch and cardiovascular stress has kept its impact as a prognostic marker also in various studies among the aged population (Wallen et al. 1997; Kistorp et al. 2005).

6.8 MMSE SCORE AND MORTALITY

In our population, the MMSE score, both as a continuous variable and using the cut-off point of 24, was a significant predictor of total mortality in all the models. In a model including other factors associated with mortality, its individual impact on mortality was only of moderate value. The predictive value of an MMSE score of less than 24 points, as studied separately and in an age- and sex-adjusted model, agreed with recently published data by Strandberg et al. (Strandberg et al. 2009) in a similar type of setting. In a multivariable model, the predictive value of this variable was somewhat reduced in our data, possibly reflecting the more extensive use of confounding variables in the survival model.

To avoid the strong prognostic implications of a diagnosis of dementia, we performed a sub-analysis after excluding the 45 individuals with dementia (all with MMSE ≥18). The value of the MMSE score was somewhat attenuated but not abolished with regard to total mortality, when the patients with an established compromised prognosis were excluded. This suggests that the prognostic importance of the MMSE score is also conveyed by other pathways than dementia. These additional mechanisms may include, for example, difficulties in engaging in health promoting activities, seeking medical advice or using the prescribed medication.

Severely reduced cognitive function, defined as an MMSE score of less than 18 points, and known dementing illness are evidently associated with severely compromised prognosis. The definition of mild cognitive impairment has varied significantly and a wide range of diagnostic approaches has been recommended (Gauthier et al. 2006). Larger epidemiological studies on the prognostic value of mild cognitive impairment have relied often on MMSE score as a diagnostic measure (Bassuk et al. 2000; Nguyen et al. 2003; Strandberg et al. 2009), and the results have been contradictory. Studies using an MMSE score of 18–23 as a definition of mild cognitive impairment have found this criterion to be a significant predictor of mortality (Bassuk et al. 2000; Strandberg et al. 2009), while a study employing another measure of cognition, the Short Portable Mental Status Questionnaire, showed no predictive value for mild cognitive impairment (Stump et al. 2001). One study suggested that the association is apparent only in individuals aged less than 80 years (Bassuk et al. 2000). The present data suggest an association with the MMSE score and mortality also among those beyond 80 years of age (data not shown).

6.9 MMSE SCORE AND CARDIOVASCULAR MORTALITY

Cognitive dysfunction has been associated with heart failure due to systolic and diastolic dysfunction (Cacciatore et al. 1998; Suwa et al. 2009), and cognitive decline has been shown to predict mortality in heart failure patients (Zuccala et al. 2003). The failure of traditional cardiovascular risk markers for the elderly, and the accumulating evidence on the association between cardiovascular burden and cognitive dysfunction have led to the hypothesis that the MMSE score might hold additional predictive value for cardiovascular mortality (Strandberg et al. 2009). Our data suggest that mild cognitive impairment as defined by an MMSE of 18–23 is associated with cardiovascular mortality when studied separately or in a sex- and age-adjusted model. In a multivariable model with known cardiovascular risk markers, with or without BNP, the MMSE score did not provide any additional prognostic information.

6.10 FUTURE PERSPECTIVES

Epidemiological studies on the elderly population are challenging due to several reasons. In studies among younger populations confounding illnesses and medications are seemingly rare, and individuals carrying/using them can be excluded, allowing for more clear conclusions about the association of the risk factor and the outcome studied. In the elderly population multiple pathological conditions are present and the use of different medications is far more common. The physiological changes associated with aging and pathological changes connected to cognitive decline further add to the complexity of the

studies. Our finding concerning the association of the mitral valve inflow pattern with non-cardiovascular mortality and the presence of dementive illness has not been reported previously. This finding should be confirmed in other studies carried out in elderly populations, and the predictive power of mitral inflow concerning non-cardiovascular mortality should also be analysed in population studies among younger individuals.

Studies tackling the most interesting aspect of daily practice, whether the occurrence of a dementive illness can be postponed or whether the prognosis of an already diseased person can be improved by influencing cardiovascular risk burden, have been rare. Such data would also disclose whether an individual cardiovascular risk factor bears a direct pathophysiological role in the development of cognitive impairment or whether it is merely a bystander reflecting an underlying process responsible for the development of dementia. Targeting this major perspective requires the launching of interventional studies with cognitive changes as primary end points, while the past analyses have almost exclusively used cognitive markers as secondary or, more frequently, tertiary end points. If the occurrence of a dementing illness can be delayed even by one year, it would constitute a remarkable difference in the suffering of the patients and their families, not forgetting the impact on economical costs at the society level. Therefore, definitive randomised double-blind studies are needed, even though funding such trials may be problematic, since the cardiovascular drugs most often applied in risk factor control are relatively inexpensive. Our finding about the connection between cognitive dysfunction and BNP adds to the body of evidence that cardiovascular morbidity and stress also significantly affect cognitive decline in the elderly population. Future studies investigating the effect of antihypertensive therapy on cognitive function in the elderly should clarify whether the concomitant decrease in BNP stratifies the risk of cognitive impairment. If so, BNP determination might identify the patients who would potentially benefit from antihypertensive therapy in the prevention of dementia.

7 Conclusions

Based on the findings of the present study, the following conclusions in a population aged 75 or more can be made:

1. In the overall study population and in the subgroup of participants with no previous heart failure, HDL cholesterol, but not BNP, shows significant correlation with left ventricular systolic dysfunction.

2. An echocardiographically measured inverted mitral inflow pattern is a robust predictor of total and non-cardiovascular mortality, with no significant connection to cardiovascular mortality.

3. BNP is an independent harbinger of cognitive decline and the incidence of new onset of dementia. This is grounds for testing the impact of antihypertensive treatment in the prevention of cognitive impairment in those with elevated BNP.

4. BNP, a measure of cardiovascular burden, and an MMSE score of 18–23, an indicator of mild cognitive impairment, are both independent predictors of total mortality. BNP, but not an MMSE score of 18–23, is independently associated to cardiovascular mortality. BNP and MMSE score may potentially be useful in screening patients for an elevated risk of mortality.

8 References

Alehagen U, Lindstedt G, Eriksson H and Dahlstrom U. 2003. Utility of the amino-terminal fragment of pro-brain natriuretic peptide in plasma for the evaluation of cardiac dysfunction in elderly patients in primary health care. Clin Chem 49: 1337-46.

Anderson C, Teo K, Gao P, Arima H, Dans A, Unger T, Commerford P, Dyal L, Schumacher H, Pogue J, Paolasso E, Holwerda N, Chazova I, Binbrek A, Young J and Yusuf S. 2011. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol 10: 43-53.

Applegate WB, Pressel S, Wittes J, Luhr J, Shekelle RB, Camel GH, Greenlick MR, Hadley E, Moye L, Perry HM, Jr. and et al. 1994. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med 154: 2154-60.

Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D and Fratiglioni L. 2008. Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. J Am Geriatr Soc 56: 111-6.

Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J and Kitzman D. 2001. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study. J Am Coll Cardiol 37: 1042-8.

Banka CL. 1996. High density lipoprotein and lipoprotein oxidation. Curr Opin Lipidol 7: 139-42.

Barrett-Connor E, Edelstein S, Corey-Bloom J and Wiederholt W. 1998. Weight loss precedes dementia in community-dwelling older adults. J Nutr Health Aging 2: 113-4.

Bassuk SS, Wypij D and Berkman LF. 2000. Cognitive Impairment and Mortality in Community-Dwelling Elderly. American Journal of Epidemiology 151: 677-688.

Bella JN, Palmieri V, Roman MJ, Liu JE, Welty TK, Lee ET, Fabsitz RR, Howard BV and Devereux RB. 2002. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. Circulation 105: 1928-33.

Bergamini C, Cicoira M, Rossi A and Vassanelli C. 2009. Oxidative stress and hyperuricaemia: pathophysiology, clinical relevance, and therapeutic implications in chronic heart failure. Eur J Heart Fail.

Biessels GJ. 1999. Cerebral complications of diabetes: clinical findings and pathogenetic mechanisms. Neth J Med 54: 35-45.

Biessels GJ, Staekenborg S, Brunner E, Brayne C and Scheltens P. 2006. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 5: 64-74.

Bodovitz S and Klein WL. 1996. Cholesterol modulates alpha-secretase cleavage of amyloid precursor protein. J Biol Chem 271: 4436-40.

Bossone E, Duong-Wagner TH, Paciocco G, Oral H, Ricciardi M, Bach DS, Rubenfire M and Armstrong WF. 1999. Echocardiographic features of primary pulmonary hypertension. J Am Soc Echocardiogr 12: 655-62.

Buerger K, Ernst A, Ewers M, Uspenskaya O, Omerovic M, Morgenthaler NG, Knauer K, Bergmann A and Hampel H. 2009. Blood-based microcirculation markers in Alzheimer's disease-diagnostic value of midregional pro-atrial natriuretic peptide/C-terminal endothelin-1 precursor fragment ratio. Biol Psychiatry 65: 979-84.

Buerger K, Uspenskaya O, Hartmann O, Hansson O, Minthon L, Blennow K, Moeller HJ, Teipel SJ, Ernst A, Bergmann A and Hampel H. 2011. Prediction of Alzheimer's disease using midregional proadrenomedullin and midregional proatrial natriuretic peptide: a retrospective analysis of 134 patients with mild cognitive impairment. J Clin Psychiatry.

Burns JM, Johnson DK, Watts A, Swerdlow RH and Brooks WM. 2010. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. Arch Neurol 67: 428-33.

Cacciatore F, Abete P, Ferrara N, Calabrese C, Napoli C, Maggi S, Varricchio M and Rengo F. 1998. Congestive heart failure and cognitive impairment in an older population. Osservatorio Geriatrico Campano Study Group. J Am Geriatr Soc 46: 1343-8.

Caselli RJ, Dueck AC, Locke DE, Sabbagh MN, Ahern GL, Rapcsak SZ, Baxter LC, Yaari R, Woodruff BK, Hoffman-Snyder C, Rademakers R, Findley S and Reiman EM. 2011. Cerebrovascular risk factors and preclinical memory decline in healthy APOE {varepsilon}4 homozygotes. Neurology.

Cataldo JK, Prochaska JJ and Glantz SA. 2010. Cigarette smoking is a risk factor for Alzheimer's Disease: an analysis controlling for tobacco industry affiliation. J Alzheimers Dis 19: 465-80.

Chong AY, Blann AD, Patel J, Freestone B, Hughes E and Lip GY. 2004. Endothelial dysfunction and damage in congestive heart failure: relation of flow-mediated dilation to circulating endothelial cells, plasma indexes of endothelial damage, and brain natriuretic peptide. Circulation 110: 1794-8.

Cockcroft DW and Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. Nephron 16: 31-41.

Cosentino S, Scarmeas N, Helzner E, Glymour MM, Brandt J, Albert M, Blacker D and Stern Y. 2008. APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. Neurology 70: 1842-9.

Court JA and Perry EK. 2003. Neurotransmitter abnormalities in vascular dementia. Int Psychogeriatr 15 Suppl 1: 81-7.

Curb JD, Rodriguez BL, Abbott RD, Petrovitch H, Ross GW, Masaki KH, Foley D, Blanchette PL, Harris T, Chen R and White LR. 1999. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. Neurology 52: 971-5.

Dalen H, Thorstensen A, Vatten LJ, Aase SA and Stoylen A. 2010. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. Circ Cardiovasc Imaging 3: 614-22.

Daniels LB and Maisel AS. 2007. Natriuretic peptides. J Am Coll Cardiol 50: 2357-68.

de Bold AJ, Borenstein HB, Veress AT and Sonnenberg H. 1981. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 28: 89-94.

de la Monte SM and Wands JR. 2005. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J Alzheimers Dis 7: 45-61.

de Leeuw FE, de Groot JC, Achten E, Oudkerk M, Ramos LM, Heijboer R, Hofman A, Jolles J, van Gijn J and Breteler MM. 2001. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 70: 9-14.

Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I and Reichek N. 1986. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 57: 450-8.

Devereux RB, Roman MJ, Palmieri V, Liu JE, Lee ET, Best LG, Fabsitz RR, Rodeheffer RJ and Howard BV. 2003. Prognostic implications of ejection fraction from linear echocardiographic dimensions: the Strong Heart Study. Am Heart J 146: 527-34.

Di Bari M, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L, Somes GW and Applegate WB. 2001. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. Am J Epidemiol 153: 72-8.

Di Carlo A, Baldereschi M, Amaducci L, Maggi S, Grigoletto F, Scarlato G and Inzitari D. 2000. Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. J Am Geriatr Soc 48: 775-82.

Dietschy JM. 2009. Central nervous system: cholesterol turnover, brain development and neurodegeneration. Biol Chem 390: 287-93.

Ebly EM, Hogan DB and Parhad IM. 1995. Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging. Arch Neurol 52: 612-9.

Ellinor PT, Low AF, Patton KK, Shea MA and Macrae CA. 2005. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. J Am Coll Cardiol 45: 82-6.

European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim (2010). London, European Medicines Agency**:** 1-2.

Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Hebert LE, Hennekens CH and Taylor JO. 1989. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. Jama 262: 2551-6.

Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, Eckman CB, Tanzi RE, Selkoe DJ and Guenette S. 2003. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. Proc Natl Acad Sci U S A 100: 4162-7.

Fassbender K, Simons M, Bergmann C, Stroick M, Lutjohann D, Keller P, Runz H, Kuhl S, Bertsch T, von Bergmann K, Hennerici M, Beyreuther K and Hartmann T. 2001. Simvastatin strongly reduces levels of Alzheimer's disease beta -amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo. Proc Natl Acad Sci U S A 98: 5856-61.

Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, Schwam E, Schindler R, Hey-Hadavi J, DeMicco DA and Breazna A. 2010. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. Neurology 74: 956-64.

Feola M, Rosso GL, Peano M, Agostini M, Aspromonte N, Carena G, Salvatico L and Valle R. 2007. Correlation between cognitive impairment and prognostic parameters in patients with congestive heart failure. Arch Med Res 38: 234-9.

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E and Scazufca M. 2005. Global prevalence of dementia: a Delphi consensus study. Lancet 366: 2112-7.

Fewlass DC, Noboa K, Pi-Sunyer FX, Johnston JM, Yan SD and Tezapsidis N. 2004. Obesity-related leptin regulates Alzheimer's Abeta. Faseb J 18: 1870-8.

Finucci G, Desideri A, Sacerdoti D, Bolognesi M, Merkel C, Angeli P and Gatta A. 1996. Left ventricular diastolic function in liver cirrhosis. Scand J Gastroenterol 31: 279-84.

Fishel MA, Watson GS, Montine TJ, Wang Q, Green PS, Kulstad JJ, Cook DG, Peskind ER, Baker LD, Goldgaber D, Nie W, Asthana S, Plymate SR, Schwartz MW and Craft S. 2005. Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults. Arch Neurol 62: 1539-44.

Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL and Tow DE. 1979. Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. A comparison of cineangiographic and radionuclide techniques. Circulation 60: 760-6.

Folstein MF, Folstein SE and McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189-98.

Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y and Fagard R. 1998. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 352: 1347-51.

Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, Robbins JA and Gardin JM. 1998. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. Jama 279: 585-92.

Friedewald WT, Levy RI and Fredrickson DS. 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18: 499-502.

Friedman JM and Halaas JL. 1998. Leptin and the regulation of body weight in mammals. Nature 395: 763-70.

Gardin JM, McClelland R, Kitzman D, Lima JA, Bommer W, Klopfenstein HS, Wong ND, Smith VE and Gottdiener J. 2001. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). Am J Cardiol 87: 1051-7.

Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P and Winblad B. 2006. Mild cognitive impairment. Lancet 367: 1262-70.

General information and national estimates on diabetes in the United States. (2005). U. S. D. o. H. a. H. Services, Centers for Disease Control and Prevention.

Go AS, Lee WY, Yang J, Lo JC and Gurwitz JH. 2006. Statin therapy and risks for death and hospitalization in chronic heart failure. Jama 296: 2105-11.

Gold M, Alderton C, Zvartau-Hind M, Egginton S, Saunders AM, Irizarry M, Craft S, Landreth G, Linnamagi U and Sawchak S. 2010. Rosiglitazone monotherapy in mild-to-moderate alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement Geriatr Cogn Disord 30: 131-46.

Greenland S. 1995. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 6: 356-65.

Gunstad J, Poppas A, Smeal S, Paul RH, Tate DF, Jefferson AL, Forman DE and Cohen RA. 2006. Relation of brain natriuretic peptide levels to cognitive dysfunction in adults > 55 years of age with cardiovascular disease. Am J Cardiol 98: 538-40.

Guo Z, Fratiglioni L, Zhu L, Fastbom J, Winblad B and Viitanen M. 1999. Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use. Arch Neurol 56: 991-6.

Guo Z, Viitanen M, Fratiglioni L and Winblad B. 1996. Low blood pressure and dementia in elderly people: the Kungsholmen project. Bmj 312: 805-8.

Gurudevan SV, Malouf PJ, Auger WR, Waltman TJ, Madani M, Raisinghani AB, DeMaria AN and Blanchard DG. 2007. Abnormal left ventricular diastolic filling in chronic thromboembolic pulmonary hypertension: true diastolic dysfunction or left ventricular underfilling? J Am Coll Cardiol 49: 1334-9.

Gustafson D, Rothenberg E, Blennow K, Steen B and Skoog I. 2003. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 163: 1524-8.

Gustafson DR, Backman K, Waern M, Ostling S, Guo X, Zandi P, Mielke MM, Bengtsson C and Skoog I. 2009. Adiposity indicators and dementia over 32 years in Sweden. Neurology 73: 1559-66.

Haag MD, Hofman A, Koudstaal PJ, Stricker BH and Breteler MM. 2009. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. J Neurol Neurosurg Psychiatry 80: 13-7.

Haan MN. 2006. Therapy Insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. Nat Clin Pract Neurol 2: 159-66.

Hanon O, Latour F, Seux ML, Lenoir H, Forette F and Rigaud AS. 2005. Evolution of blood pressure in patients with Alzheimer's disease: a one year survey of a French Cohort (REAL.FR). J Nutr Health Aging 9: 106-11.

Harrell FE, Jr., Lee KL and Mark DB. 1996. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15: 361-87.

Harvey J, Solovyova N and Irving A. 2006. Leptin and its role in hippocampal synaptic plasticity. Prog Lipid Res 45: 369-78.

Hayashi H. 2011. Lipid metabolism and glial lipoproteins in the central nervous system. Biol Pharm Bull 34: 453-61.

Hebert LE, Scherr PA, Bennett DA, Bienias JL, Wilson RS, Morris MC and Evans DA. 2004. Blood pressure and late-life cognitive function change: a biracial longitudinal population study. Neurology 62: 2021-4.

Hebert LE, Scherr PA, Bienias JL, Bennett DA and Evans DA. 2003. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 60: 1119-22.

Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW and Shekelle PG. 2004. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol 43: 1019-26.

Hernan MA, Alonso A and Logroscino G. 2008. Cigarette smoking and dementia: potential selection bias in the elderly. Epidemiology 19: 448-50.

Hiitola PK, Enlund H, Sulkava RO and Hartikainen SA. 2007. Changes in the use of cardiovascular medicines in the elderly aged 75 years or older--a population-based Kuopio 75+ study. J Clin Pharm Ther 32: 253-9.

Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, Go AS, Harrell FE, Jr., Hong Y, Howard BV, Howard VJ, Hsue PY, Kramer CM, McConnell JP, Normand SL, O'Donnell CJ, Smith SC, Jr. and Wilson PW. 2009. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 119: 2408-16.

Hoglund K, Wallin A and Blennow K. 2006. Effect of statins on beta-amyloid metabolism in humans: potential importance for the development of senile plaques in Alzheimer's disease. Acta Neurol Scand Suppl 185: 87-92.

Iadecola C. 2004. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci 5: 347-60.

Iadecola C and Davisson RL. 2008. Hypertension and cerebrovascular dysfunction. Cell Metab 7: 476-84.

Inoko M, Fujita M, Nakae I, Tamaki S, Watanuki M, Hashimoto T and Konishi T. 2001. Effect of angiotensin-converting enzyme inhibition on sympathetic tone in patients with mild to moderate heart failure. Jpn Circ J 65: 395-8.

Jagger C, Andersen K, Breteler MM, Copeland JR, Helmer C, Baldereschi M, Fratiglioni L, Lobo A, Soininen H, Hofman A and Launer LJ. 2000. Prognosis with dementia in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 54: S16-20.

Jick H, Zornberg GL, Jick SS, Seshadri S and Drachman DA. 2000. Statins and the risk of dementia. Lancet 356: 1627-31.

Johnson DK, Wilkins CH and Morris JC. 2006. Accelerated weight loss may precede diagnosis in Alzheimer disease. Arch Neurol 63: 1312-7.

Kardys I, Deckers JW, Stricker BH, Vletter WB, Hofman A and Witteman JC. 2009. Echocardiographic parameters and all-cause mortality: the Rotterdam Study. Int J Cardiol 133: 198-204.

Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK and He J. 2005. Global burden of hypertension: analysis of worldwide data. Lancet 365: 217-23.

Kelman HR, Thomas C, Kennedy GJ and Cheng J. 1994. Cognitive impairment and mortality in older community residents. Am J Public Health 84: 1255-60.

Kerola T, Kettunen R and Nieminen T. 2011. The complex interplay of cardiovascular system and cognition: How to predict dementia in the elderly? Int J Cardiol 150: 123-129.

Kerola T, Lehtimäki T, Kähönen M and Nieminen T. 2010. Statin pharmacogenomics: Lipid Response and Cardiovascular Outcomes. Current Cardiovascular Risk Reports 4: 150-158.

Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J and Hildebrandt P. 2005. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. Jama 293: 1609-16.

Kivipelto M, Helkala EL, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J and Nissinen A. 2001. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology 56: 1683-9.

Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Iivonen S, Mannermaa A, Tuomilehto J, Nissinen A and Soininen H. 2002. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med 137: 149-55.

Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J and Nissinen A. 2001. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. Bmj 322: 1447-51.

Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H and Nissinen A. 2005. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 62: 1556-60.

Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janosi A, Kamensky G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H and Wikstrand J. 2007. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 357: 2248-61.

Kloppenborg RP, van den Berg E, Kappelle LJ and Biessels GJ. 2008. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol 585: 97-108.

Knopman DS, Edland SD, Cha RH, Petersen RC and Rocca WA. 2007. Incident dementia in women is preceded by weight loss by at least a decade. Neurology 69: 739-46.

Kondziella D, Gothlin M, Fu M, Zetterberg H and Wallin A. 2009. B-type natriuretic peptide plasma levels are elevated in subcortical vascular dementia. Neuroreport 20: 825-7.

Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, Fitzpatrick A, Fried L and Haan MN. 2003. Risk factors for dementia in the cardiovascular health cognition study. Neuroepidemiology 22: 13-22.

Kupari M, Lindroos M, Iivanainen AM, Heikkila J and Tilvis R. 1997. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med 241: 387-94.

Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L and Kukull WA. 2004. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med 140: 501-9.

Latini R, Masson S, Anand I, Judd D, Maggioni AP, Chiang YT, Bevilacqua M, Salio M, Cardano P, Dunselman PH, Holwerda NJ, Tognoni G and Cohn JN. 2002. Effects of valsartan on circulating brain natriuretic peptide and norepinephrine in symptomatic chronic heart failure: the Valsartan Heart Failure Trial (Val-HeFT). Circulation 106: 2454-8.

Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR and Havlik RJ. 2000. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 21: 49-55.

Leibson CL, Rocca WA, Hanson VA, Cha R, Kokmen E, O'Brien PC and Palumbo PJ. 1997. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. Am J Epidemiol 145: 301-8.

Levy D, Garrison RJ, Savage DD, Kannel WB and Castelli WP. 1990. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 322: 1561-6.

Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE and Wolozin B. 2010. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. Bmj 340: b5465.

Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, Harris TB, Roubenoff R, Auerbach S, DeCarli C, Wolf PA and Seshadri S. 2009. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. Jama 302: 2565-72.

Loke I, Squire IB, Davies JE and Ng LL. 2003. Reference ranges for natriuretic peptides for diagnostic use are dependent on age, gender and heart rate. Eur J Heart Fail 5: 599-606.

Luchner A, Burnett JC, Jr., Jougasaki M, Hense HW, Heid IM, Muders F, Riegger GA and Schunkert H. 2000. Evaluation of brain natriuretic peptide as marker of left ventricular dysfunction and hypertrophy in the population. J Hypertens 18: 1121-8.

Luchsinger JA, Patel B, Tang MX, Schupf N and Mayeux R. 2007. Measures of adiposity and dementia risk in elderly persons. Arch Neurol 64: 392-8.

Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ and Mayeux R. 2007. Relation of diabetes to mild cognitive impairment. Arch Neurol 64: 570-5.

Luchsinger JA, Tang MX, Shea S and Mayeux R. 2004. Hyperinsulinemia and risk of Alzheimer disease. Neurology 63: 1187-92.

Macdonald JE, Kennedy N and Struthers AD. 2004. Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other

prognostic markers in patients with mild heart failure already taking optimal treatment. Heart 90: 765-70.

Mahley RW. 1988. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 240: 622-30.

Manschot SM, Biessels GJ, de Valk H, Algra A, Rutten GE, van der Grond J and Kappelle LJ. 2007. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. Diabetologia 50: 2388-97.

McGuinness B, Craig D, Bullock R and Passmore P. 2009. Statins for the prevention of dementia. Cochrane Database Syst Rev: CD003160.

McGuinness B, Todd S, Passmore AP and Bullock R. 2009. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. Cochrane Database Syst Rev. 4: CD:004034.

McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA and Perry RH. 1996. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47: 1113-24.

Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC and Frohlich ED. 2004. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 43: 1590-5.

Meyer JS, Rauch GM, Crawford K, Rauch RA, Konno S, Akiyama H, Terayama Y and Haque A. 1999. Risk factors accelerating cerebral degenerative changes, cognitive decline and dementia. Int J Geriatr Psychiatry 14: 1050-61.

Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B and Skoog I. 2005. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology 64: 1689-95.

Miles W and Root H. 1922. Psychologic tests applies to diabetic patients. Arch Intern Med 30: 767-7.

Molyneux SL, Florkowski CM, George PM, Pilbrow AP, Frampton CM, Lever M and Richards AM. 2008. Coenzyme Q10: an independent predictor of mortality in chronic heart failure. J Am Coll Cardiol 52: 1435-41.

Morley JE. 2002. Nutrition in the elderly. Curr Opin Gastroenterol 18: 240-5.

Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA and Evans DA. 2001. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol 58: 1640-6.

Mueller WH, Wear ML, Hanis CL, Emerson JB, Barton SA, Hewett-Emmett D and Schull WJ. 1991. Which measure of body fat distribution is best for epidemiologic research? Am J Epidemiol 133: 858-69.

Murray KN and Abeles N. 2002. Nicotine's effect on neural and cognitive functioning in an aging population. Aging Ment Health 6: 129-38.

Naito J, Naka Y and Watanabe H. 2009. Clinical impression of brain natriuretic peptide levels in demented patients without cardiovascular disease. Geriatr Gerontol Int 9: 242-5.

Naor M, Steingruber HJ, Westhoff K, Schottenfeld-Naor Y and Gries AF. 1997. Cognitive function in elderly non-insulin-dependent diabetic patients before and after inpatient treatment for metabolic control. J Diabetes Complications 11: 40-6.

Nguyen HT, Black SA, Ray LA, Espino DV and Markides KS. 2003. Cognitive impairment and mortality in older mexican americans. J Am Geriatr Soc 51: 178-83.

Nieminen T, Kahonen M, Viiri LE, Gronroos P and Lehtimaki T. 2008. Pharmacogenetics of apolipoprotein E gene during lipid-lowering therapy: lipid levels and prevention of coronary heart disease. Pharmacogenomics 9: 1475-86.

Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, Tuomilehto J and Nissinen A. 1998. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology 17: 14-20.

Nourhashemi F, Deschamps V, Larrieu S, Letenneur L, Dartigues JF and Barberger-Gateau P. 2003. Body mass index and incidence of dementia: the PAQUID study. Neurology 60: 117-9.

Nourhashemi F and Vellas B. 2008. Weight loss as a predictor of dementia and Alzheimer's disease? Expert Rev Neurother 8: 691-3.

Oates DJ, Berlowitz DR, Glickman ME, Silliman RA and Borzecki AM. 2007. Blood pressure and survival in the oldest old. J Am Geriatr Soc 55: 383-8.

Ogawa Y, Nakao K, Mukoyama M, Shirakami G, Itoh H, Hosoda K, Saito Y, Arai H, Suga S, Jougasaki M and et al. 1990. Rat brain natriuretic peptide--tissue distribution and molecular form. Endocrinology 126: 2225-7.

Oh JK, Hatle L, Tajik AJ and Little WC. 2006. Diastolic heart failure can be diagnosed by comprehensive two-dimensional and Doppler echocardiography. J Am Coll Cardiol 47: 500-6.

Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM and Tajik AJ. 2000. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 102: 1788-94.

Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE and Breteler MM. 1996. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia 39: 1392-7.

Park CR. 2001. Cognitive effects of insulin in the central nervous system. Neurosci Biobehav Rev 25: 311-23.

Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R and Travert F. 2008. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358: 2560-72.

Pedersen T, Kjekshus J, Berg K, Haghfelt T, Faegerman O, Thorgeirsson G, Pyörälä K, Miettinen T, Wilhemsen L, Olsson A and Wedel H. 1994. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344: 1383-9.

Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, Comsa M, Burch L, Fletcher A and Bulpitt C. 2008. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 7: 683-9.

Peters R, Poulter R, Beckett N, Forette F, Fagard R, Potter J, Swift C, Anderson C, Fletcher A and Bulpitt CJ. 2009. Cardiovascular and biochemical risk factors for incident dementia in the Hypertension in the Very Elderly Trial. J Hypertens 27: 2055-62.

Peters R, Poulter R, Warner J, Beckett N, Burch L and Bulpitt C. 2008. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr 8: 36.

Pfrieger FW. 2003. Cholesterol homeostasis and function in neurons of the central nervous system. Cell Mol Life Sci 60: 1158-71.

Posner HB, Tang MX, Luchsinger J, Lantigua R, Stern Y and Mayeux R. 2002. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology 58: 1175-81.

Price KA. 2010. Hydration in cancer patients. Curr Opin Support Palliat Care 4: 276-80.

Pulliainen V, Hänninen T and Hokkanen L. 2007. Norms for use of the CERAD test battery in Finland (in Finnish). Suomen LääkL 62: 1235-1241.

Pyörälä K, Salonen JT and Valkonen T. 1985. Trends in coronary heart disease mortality and morbidity and related factors in FInland.
Cardiology 72: 35-51.

Qiu C, von Strauss E, Fastbom J, Winblad B and Fratiglioni L. 2003. Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. Arch Neurol 60: 223-8.

Qiu C, Winblad B and Fratiglioni L. 2005. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 4: 487-99.

Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, Coats AJ and Anker SD. 2003. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol 42: 1933-40.

Rauchhaus M, Coats AJ and Anker SD. 2000. The endotoxin-lipoprotein hypothesis. Lancet 356: 930-3.

Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR and Rodeheffer RJ. 2003. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. Jama 289: 194-202.

Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR and Burnett JC, Jr. 2002. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 40: 976-82.

Richards AM. 2007. Natriuretic peptides: update on Peptide release, bioactivity, and clinical use. Hypertension 50: 25-30.

Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, Zvartau-Hind ME, Hosford DA and Roses AD. 2006. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J 6: 246-54.

Roberts RO, Geda YE, Knopman DS, Christianson TJ, Pankratz VS, Boeve BF, Vella A, Rocca WA and Petersen RC. 2008. Association of duration and severity of diabetes mellitus with mild cognitive impairment. Arch Neurol 65: 1066-73.

Ronnemaa E, Zethelius B, Sundelof J, Sundstrom J, Degerman-Gunnarsson M, Berne C, Lannfelt L and Kilander L. 2008. Impaired insulin secretion increases the risk of Alzheimer disease. Neurology 71: 1065-71.

Roques F, Michel P, Goldstone AR and Nashef SA. 2003. The logistic EuroSCORE. Eur Heart J 24: 881-2.

Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, van Harskamp F, Hofman A and Breteler MM. 2001. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. Dement Geriatr Cogn Disord 12: 33-9.

Rusanen M, Kivipelto M, Quesenberry CP, Jr., Zhou J and Whitmer RA. 2011. Heavy Smoking in Midlife and Long-term Risk of Alzheimer Disease and Vascular Dementia. Arch Intern Med 171: 333-339.

Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR and Strachan MW. 2006. Improving metabolic control leads to better working memory in adults with type 2 diabetes. Diabetes Care 29: 345-51.

Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR and Braunwald E. 1996. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 335: 1001-9.

Sadek MM, Haddad T and Haddad H. 2009. The role of statins in chronic heart failure. Curr Opin Cardiol 24: 167-71.

Sahn DJ, DeMaria A, Kisslo J and Weyman A. 1978. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 58: 1072-83.

Salerno F, Cazzaniga M, Pagnozzi G, Cirello I, Nicolini A, Meregaglia D and Burdick L. 2003. Humoral and cardiac effects of TIPS in cirrhotic patients with different "effective" blood volume. Hepatology 38: 1370-7.

Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ and et al. 1993. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43: 1467-72.

Scarborough P, Bhatnagar P, Wickramasinghe K, Smolina K, C M and Rayner M (2010). Coronary heart disease statistics 2010 edition, British Heart Foundation.

Scarmeas N, Stern Y, Tang MX, Mayeux R and Luchsinger JA. 2006. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 59: 912-21.

Schupf N, Costa R, Luchsinger J, Tang MX, Lee JH and Mayeux R. 2005. Relationship between plasma lipids and all-cause mortality in nondemented elderly. J Am Geriatr Soc 53: 219-26.

Silbert LC, Howieson DB, Dodge H and Kaye JA. 2009. Cognitive impairment risk: white matter hyperintensity progression matters. Neurology 73: 120-5.

Simons M, Keller P, De Strooper B, Beyreuther K, Dotti CG and Simons K. 1998. Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. Proc Natl Acad Sci U S A 95: 6460-4.

Sink KM, Leng X, Williamson J, Kritchevsky SB, Yaffe K, Kuller L, Yasar S, Atkinson H, Robbins M, Psaty B and Goff DC, Jr. 2009. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the cardiovascular health study. Arch Intern Med 169: 1195-202.

Skoog I, Lithell H, Hansson L, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P and Zanchetti A. 2005. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). Am J Hypertens 18: 1052-9.

Smith H, Pickering RM, Struthers A, Simpson I and Mant D. 2000. Biochemical diagnosis of ventricular dysfunction in elderly patients in general practice: observational study. Bmj 320: 906-8.

Smith LL. 1991. Another cholesterol hypothesis: cholesterol as antioxidant. Free Radic Biol Med 11: 47-61.

Sola S, Mir MQ, Lerakis S, Tandon N and Khan BV. 2006. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol 47: 332-7.

Solomon A, Kareholt I, Ngandu T, Winblad B, Nissinen A, Tuomilehto J, Soininen H and Kivipelto M. 2007. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology 68: 751-6.

Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR and Launer LJ. 2005. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol 62: 55-60.

Strandberg TE, Pitkala KH and Tilvis RS. 2009. Predictors of mortality in home-dwelling patients with cardiovascular disease aged 75 and older. J Am Geriatr Soc 57: 279-84.

Strandberg TE and Tilvis RS. 2000. C-reactive protein, cardiovascular risk factors, and mortality in a prospective study in the elderly. Arterioscler Thromb Vasc Biol 20: 1057-60.

Stump TE, Callahan CM and Hendrie HC. 2001. Cognitive impairment and mortality in older primary care patients. J Am Geriatr Soc 49: 934-40.

Sudoh T, Kangawa K, Minamino N and Matsuo H. 1988. A new natriuretic peptide in porcine brain. Nature 332: 78-81.

Suwa M and Ito T. 2009. Correlation between cognitive impairment and left ventricular diastolic dysfunction in patients with cardiovascular diseases. Int J Cardiol 136: 351-4.

Sviridov D, Mukhamedova N, Remaley A, Chin-Dusting J and Nestel P. 2008. Antiatherogenic Functionality of High Density Lipoprotein: How Much versus How Good. J Atheroscler Thromb 15: 52-62.

Takata Y, Ansai T, Soh I, Akifusa S, Sonoki K, Fujisawa K, Awano S, Kagiyama S, Hamasaki T, Nakamichi I, Yoshida A and Takehara T. 2007. Association between body mass index and mortality in an 80-year-old population. J Am Geriatr Soc 55: 913-7.

Talini E, Di Bello V, Bianchi C, Palagi C, Delle Donne MG, Penno G, Nardi C, Canale ML, Del Prato S, Mariani M and Miccoli R. 2008. Early impairment of left ventricular function in hypercholesterolemia and its reversibility after short term treatment with rosuvastatin A preliminary echocardiographic study. Atherosclerosis 197: 346-54.

Tang WH, Francis GS, Morrow DA, Newby LK, Cannon CP, Jesse RL, Storrow AB, Christenson RH, Apple FS, Ravkilde J and Wu AH. 2007. National Academy of Clinical

Biochemistry Laboratory Medicine practice guidelines: Clinical utilization of cardiac biomarker testing in heart failure. Circulation 116: e99-109.

Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M and Tognoni G. 2008. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. Lancet 372: 1231-39.

Tervo S, Kivipelto M, Hanninen T, Vanhanen M, Hallikainen M, Mannermaa A and Soininen H. 2004. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement Geriatr Cogn Disord 17: 196-203.

Vaisar T, Pennathur S, Green PS, Gharib SA, Hoofnagle AN, Cheung MC, Byun J, Vuletic S, Kassim S, Singh P, Chea H, Knopp RH, Brunzell J, Geary R, Chait A, Zhao XQ, Elkon K, Marcovina S, Ridker P, Oram JF and Heinecke JW. 2007. Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. J Clin Invest 117: 746-56.

van den Berg E, Biessels GJ, de Craen AJ, Gussekloo J and Westendorp RG. 2007. The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. Neurology 69: 979-85.

Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hanninen T, Soininen H, Kervinen K, Kesaniemi YA, Laakso M and Kuusisto J. 2006. Association of metabolic syndrome with Alzheimer disease: a population-based study. Neurology 67: 843-7.

Vanhanen M, Kuusisto J, Koivisto K, Mykkanen L, Helkala EL, Hanninen T, Riekkinen P, Sr., Soininen H and Laakso M. 1999. Type-2 diabetes and cognitive function in a non-demented population. Acta Neurol Scand 100: 97-101.

Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW and Levy D. 2002. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. Jama 288: 1252-9.

Vekrellis K, Ye Z, Qiu WQ, Walsh D, Hartley D, Chesneau V, Rosner MR and Selkoe DJ. 2000. Neurons regulate extracellular levels of amyloid beta-protein via proteolysis by insulin-degrading enzyme. J Neurosci 20: 1657-65.

Veld BA, Ruitenberg A, Hofman A, Stricker BH and Breteler MM. 2001. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 22: 407-12.

Verdelho A, Madureira S, Moleiro C, Ferro JM, Santos CO, Erkinjuntti T, Pantoni L, Fazekas F, Visser M, Waldemar G, Wallin A, Hennerici M and Inzitari D. 2010. White matter changes and diabetes predict cognitive decline in the elderly: The LADIS Study. Neurology 75: 160-167.

Verghese J, Lipton RB, Hall CB, Kuslansky G and Katz MJ. 2003. Low blood pressure and the risk of dementia in very old individuals. Neurology 61: 1667-72.

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC and Vandenbroucke JP. 2007. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 147: 573-7.

Vuolteenaho O, Ala-Kopsala M and Ruskoaho H. 2005. BNP as a biomarker in heart disease. Adv Clin Chem 40: 1-36.

Vuolteenaho O, Arjamaa O and Ling N. 1985. Atrial natriuretic polypeptides (ANP): rat atria store high molecular weight precursor but secrete processed peptides of 25-35 amino acids. Biochem Biophys Res Commun 129: 82-8.

Vuolteenaho O, Koistinen P, Martikkala V, Takala T and Leppaluoto J. 1992. Effect of physical exercise in hypobaric conditions on atrial natriuretic peptide secretion. Am J Physiol 263: R647-52.

Waldreus N, Sjostrand F and Hahn RG. 2010. Thirst in the elderly with and without heart failure. Arch Gerontol Geriatr Epub ahead of print.

Wallen T, Landahl S, Hedner T, Hall C, Saito Y and Nakao K. 1997. Atrial natriuretic peptides predict mortality in the elderly. J Intern Med 241: 269-75.

Wallen T, Landahl S, Hedner T, Nakao K and Saito Y. 1997. Brain natriuretic peptide predicts mortality in the elderly. Heart 77: 264-7.

Wang TD, Lee CM, Wu CC, Lee TM, Chen WJ, Chen MF, Liau CS, Sung FC and Lee YT. 1999. The effects of dyslipidemia on left ventricular systolic function in patients with stable angina pectoris. Atherosclerosis 146: 117-24.

Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC and Vasan RS. 2003. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 108: 977-82.

Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA and Vasan RS. 2004. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 350: 655-63.

Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW and Vasan RS. 2004. Impact of obesity on plasma natriuretic peptide levels. Circulation 109: 594-600.

Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, Fishel MA, Kulstad JJ, Green PS, Cook DG, Kahn SE, Keeling ML and Craft S. 2005. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. Am J Geriatr Psychiatry 13: 950-8.

Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE and Westendorp RG. 1997. Total cholesterol and risk of mortality in the oldest old. Lancet 350: 1119-23.

Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, Jr. and Yaffe K. 2005. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. Bmj 330: 1360.

Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Jr. and Selby JV. 2009. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. Jama 301: 1565-72.

Whitmer RA, Sidney S, Selby J, Johnston SC and Yaffe K. 2005. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 64: 277-81.

Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H and Kannel WB. 1998. Prediction of coronary heart disease using risk factor categories. Circulation 97: 1837-47.

Xu W, Qiu C, Gatz M, Pedersen NL, Johansson B and Fratiglioni L. 2009. Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. Diabetes 58: 71-7.

Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer RA and West N. 2007. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc 55: 758-62.

Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, Tylavsky FA and Newman AB. 2004. The metabolic syndrome, inflammation, and risk of cognitive decline. Jama 292: 2237-42.

Yaffe K, Weston AL, Blackwell T and Krueger KA. 2009. The metabolic syndrome and development of cognitive impairment among older women. Arch Neurol 66: 324-8.

Yamaguchi H, Yoshida J, Yamamoto K, Sakata Y, Mano T, Akehi N, Hori M, Lim YJ, Mishima M and Masuyama T. 2004. Elevation of plasma brain natriuretic peptide is a hallmark of diastolic heart failure independent of ventricular hypertrophy. J Am Coll Cardiol 43: 55-60.

Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M and Nakao K. 1994. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 90: 195-203.

Ylikoski R, Ylikoski A, Erkinjuntti T, Sulkava R, Raininko R and Tilvis R. 1993. White matter changes in healthy elderly persons correlate with attention and speed of mental processing. Arch Neurol 50: 818-24.

Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K and et al. 1995. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 45: 1161-8.

Yoshizawa A, Yoshikawa T, Nakamura I, Satoh T, Moritani K, Suzuki M, Baba A, Iwanaga S, Mitamura H and Ogawa S. 2004. Brain natriuretic peptide response is heterogeneous during beta-blocker therapy for congestive heart failure. J Card Fail 10: 310-5.

Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A and Bernabei R. 1997. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. J Neurol Neurosurg Psychiatry 63: 509-12.

Zuccala G, Pedone C, Cesari M, Onder G, Pahor M, Marzetti E, Lo Monaco MR, Cocchi A, Carbonin P and Bernabei R. 2003. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. Am J Med 115: 97-103.

Zung WW. 1965. A self-rating Depression Scale. Arch Gen Psychiatry 12: 63-70.

Tuomas Kerola

The Interplay of Cardiovascular Burden with Cognition and Mortality

The impact of B-type natriuretic peptide (BNP), the Mini Mental State Examination score and echocardiographical measures on cognitive decline and mortality in the elderly general population was evaluated in the present study. While traditional cardiovascular risk markers failed to predict cognitive decline, BNP, marker of the burden of the heart ventricle, was solidly associated with cognitive decline and mortality. Future studies investigating the effect of antihypertensive therapy on cognitive function in the elderly should clarify whether the concomitant decrease in BNP stratifies the risk of cognitive impairment.

UNIVERSITY OF
EASTERN FINLAND

Publications of the University of Eastern Finland
Dissertations in Health Sciences

ISBN 978-952-61-0540-6