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Miika Vuorinen

Cardiovascular Risk Factors and Dementia-related Structural Brain Changes on MRI

A 30-year Follow-up Study

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Author's address: Department of Neurology, Institute of Clinical Medicine, School of Medicine
University of Eastern Finland
KUOPIO
FINLAND

Supervisors: Professor Miia Kivipelto, M.D., Ph.D.
Department of Neurology, Institute of Clinical Medicine, School of Medicine
University of Eastern Finland
KUOPIO
FINLAND
Center for Alzheimer Research, Division for Neurogeriatrics
Department of Neurobiology, Care Sciences and Society
Karolinska Institute
STOCKHOLM
SWEDEN

Professor Hilkka Soininen, M.D., Ph.D.
Department of Neurology, Institute of Clinical Medicine, School of Medicine
University of Eastern Finland
KUOPIO
FINLAND

Adjunct Professor Alina Solomon, M.D., Ph.D.
Department of Neurology, Institute of Clinical Medicine, School of Medicine
University of Eastern Finland
KUOPIO
FINLAND
Center for Alzheimer Research, Division for Neurogeriatrics
Department of Neurobiology, Care Sciences and Society
Karolinska Institute
STOCKHOLM
SWEDEN

Gabriela Spulber, M.D., Ph.D.
Division of Clinical Geriatrics
Department of Neurobiology, Care Sciences and Society
Karolinska Institute
STOCKHOLM
SWEDEN

Reviewers: Professor Nenad Bogdanovic, M.D., Ph.D
Department of Geriatric Medicine, Institute of Clinical Medicine, Faculty of Medicine
University of Oslo
OSLO
NORWAY

Associate Professor Martin Ingelsson, M.D., Ph.D.
Molecular Geriatrics / Rudbeck Laboratory, Department of Public Health and Caring Sciences, Faculty of Medicine
University of Uppsala
UPPSALA
SWEDEN

Opponent:

Niels Prins, M.D., Ph.D.
Alzheimer Center and Department of Neurology
VU University Medical Center
AMSTERDAM
THE NETHERLANDS

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ABSTRACT

Cardiovascular risk factors and conditions have been associated with an increased risk of dementia, but the mechanisms and mediating pathways are not fully understood. The present thesis focuses on the long-term relationships between blood pressure, body mass index (BMI), cholesterol, coronary heart disease (CHD) and dementia-related structural brain changes on magnetic resonance images (MRI). An additional aim was to investigate the associations between midlife CAIDE Dementia Risk Score and brain changes on MRI.

The thesis is based on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study. CAIDE participants were derived from random, population-based samples surveyed in 1972, 1977, 1982 or 1987 (midlife examination). They were re-examined 21 years later in 1998, and again in 2005-2008. The MRI populations included a group of 112 participants in 1998 re-examination, and a different group of 69 participants in 2005-2008 re-examination. Robust visual rating and novel automatic segmentation methods were used to determine structural brain changes on MRI.

Midlife and long-standing hypertension and overweight/obesity were associated with more severe white matter lesions (WML) at older ages. Midlife hypertension was also related to thinner cerebral cortex 30 years later. Declining blood pressure from midlife to late-life was related to more severe WML, and to thinner cortex in regions involved in blood pressure regulation. Long-term CHD was associated with lower total gray matter volume and thinner cortex, and this relationship was influenced by changes in blood pressure over time. CAIDE Dementia Risk Score in midlife was most consistently associated with WML later in life, and a relationship with medial temporal lobe atrophy (MTA) was observed in individuals with longer follow-up times.

These results indicate that early and sustained control of vascular risk factors may lead to a lower likelihood of cerebrovascular or neurodegenerative brain changes as the individual ages. It is also important to consider the possibility of a potential bidirectional association between vascular factors and brain changes. The CAIDE Dementia Risk Score, a simple and readily available tool for estimating dementia risk, seems to indicate even increased risk of developing cerebrovascular or typical Alzheimer pathologies.

National Library of Medical Classification: WL 358.5, WL 355, WL 307, WG 142, WL 141.5.M2
Medical Subjects Headings: Dementia; Mild Cognitive Impairment; Blood Pressure; Body Mass Index; Cardiovascular Diseases; Risk Factors; Magnetic Resonance Imaging; Brain/pathology; Cerebral Cortex/pathology; Longitudinal Studies

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TIIVISTELMÄ

Sydän- ja verisuonitaudit sekä niiden riskitekijät lisäävät riskiä sairastua dementiaan, mutta taustalla olevat mekanismit ovat osittain epäselviä. Tämän väitöskirjatyön tavoitteena oli selvittää verenpaineen, painoindeksin, kokonaiskolesterolin ja sepelvaltimotaudin pitkäaikaista yhteyttä magneettikuvissa (MRI) nähtäviin dementiaan liittyviin rakenteellisiin aivomuutoksiin. Lisäksi väitöskirjassa tarkasteltiin keski-iän CAIDE dementia-riskimittarin yhteyttä aivojen rakenteellisiin muutoksiin myöhemmällä iällä.

Väitöskirja pohjautuu suomalaiseen Kardiovaskulaariset riskitekijät, ikääntyminen ja dementia (CAIDE) tutkimukseen. CAIDE-tutkimukseen osallistujat valittiin satunnaisesti Pohjois-Karjala projektin ja FINMONICA-tutkimuksen vuosien 1972, 1977, 1982 ja 1987 neljästä itsenäisestä väestöotannasta. Valitut henkilöt tutkittiin uudelleen 21 vuotta myöhemmin vuonna 1998 ja toisen kerran vuosina 2005-2008. Vuoden 1998 MRI-aineiston muodosti 112 tutkimushenkilöä ja vuosien 2005-2008 MRI-aineiston muodosti toiset 69 henkilöä. Aivojen rakenteelliset muutokset magneettikuvissa arvioitiin perinteisiä visuaalisia sekä uudempia automaattisia menetelmiä käyttäen.

Keski-iässä sekä seurannassa koholla ollut verenpaine ja ylipaino/lihavuus olivat yhteydessä aivojen valkean aineen muutoksiin myöhemmällä iällä. Keski-iän kohonnut verenpaine oli myös yhteydessä aivojen kuorikerroksen ohentumiseen 30 vuotta myöhemmin. Verenpaineen lasku seurannan aikana lisäsi riskiä valkean aineen muutoksille sekä kuorikerroksen ohentumiselle erityisesti verenpaineen säätelyyn vaikuttavilla alueilla. Pitkäkestoinen sepelvaltimotauti oli yhteydessä harmaan aineen sekä aivojen kuorikerroksen pienentymiseen ja verenpaineen muutoksilla oli merkittävä vaikutus tähän yhteyteen. Keski-iän CAIDE dementia-riskimittarin pisteytys oli yhteydessä valkean aineen sekä sisemmän ohimolohkon muutoksiin myöhemmällä iällä.

Sydän- ja verisuonisairauksien riskitekijöiden hoidolla voidaan mahdollisesti vaikuttaa aivoverisuonisairauksien ja aivohermojen rappeutumiseen liittyvien aivomuutosten kehittymiseen. Yksinkertaista ja helposti saatavilla olevaa CAIDE dementia-riskimittaria voidaan käyttää myös aivomuutosten riskiä arvioidessa.

Luokitus: WL 358.5, WL 355, WL 307, WG 142, WL 141.5.M2
Yleinen suomalainen asiasanasto: dementia; muistihäiriöt; verenpaine; painoindeksi; sepelvaltimotauti; riskitekijät; magneettitutkimus; aivokuori

To Heidi & Mimosa

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Kuopio, May 2014

Miika Vuorinen

List of the original publications

This thesis is based on the following original publications:

I Vuorinen M, Solomon A, Rovio S, Nieminen L, Kareholt I, Tuomilehto J, Soininen H, Kivipelto M. Changes in vascular risk factors from midlife to late-life and white matter lesions: a 20- year follow-up study. *Dementia and Geriatic Cognitive Disorders 31: 119-125, 2011.*

II Vuorinen M, Kareholt I, Julkunen V, Spulber G, Niskanen E, Paajanen T, Soininen H, Kivipelto M, Solomon A. Changes in vascular factors 28 years from midlife and late-life cortical thickness. *Neurobiology of Aging 34: 100-109, 2013.*

III Vuorinen M, Damangir S, Niskanen E, Miralbell J, Rusanen M, Spulber G, Soininen H, Kivipelto M, Solomon A. Coronary heart disease and cortical thickness, gray matter and white matter lesion volumes on MRI. *Submitted for publication.*

IV Vuorinen M, Spulber G, Damangir S, Niskanen E, Ngandu T, Soininen H, Kivipelto M, Solomon A. Midlife CAIDE Dementia Risk Score and dementia-related brain changes up to 30 years later on MRI. *Submitted for publication.*

Contents

Abbreviations

Aβ	amyloid beta protein
ADDTC	Alzheimer's Disease Diagnostic and Treatment Center
ADH	anti-diuretic hormone
AF	atrial fibrillation
AIC	anterior insular cortex
ApoE	Apolipoprotein E (protein)
APOE	Apolipoprotein E (gene)
APP	amyloid precursor protein
ARWMC	Age-Related White Matter Changes
AUC	area under curve
BDRI	Brief Dementia Risk Index
BGWML	basal ganglia white matter lesions
BMI	body mass index
BP	blood pressure
CAA	cerebral amyloid angiopathy
CAC	coronary artery calcification
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CBF	cerebral blood flow
CDR	clinical dementia rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHD	coronary heart disease
CHOD-PAP	cholesterol oxidase/p-aminophenazone
CHS	Cardiovascular Health Study
CI	confidence interval
CLASP	Constrained Laplacian-based Automated Segmentation with Proximities
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computerized tomography
CVD	cerebrovascular disease
DBP	diastolic blood pressure
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
DWML	deep white matter lesions
EC	entorhinal cortex
EDPI	European Dementia Prevention Initiative
EVA	Etude du Vieillissement Artériel
FA	flip angle
FDG-PET	**f**luorodeoxyglucose positron emission tomography

FDR	false discovery rate
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FINMONICA	Finnish part of Monitoring Trends and Determinants in Cardiovascular Disease
FLAIR	Fluid Attenuated Inversion Recovery
FOV	field of view
GM	gray matter
GMS	gray matter surface
HAAS	Honolulu-Asia Aging Study
HDL	high density lipoprotein
HDR	Hospital Discharge Register
HF	heart failure
IFG	inferior frontal gyrus
IPS	intraparietal sulcus
ITWML	infratentorial white matter lesions
IWG	International Working Group
kg	kilogram
LDL	low density lipoprotein
m	meter
MAPT	Multidomain Alzheimer Preventive Trial
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MTA	medial temporal lobe atrophy
NFT	neurofibrillary tangle
NHLBI	National Heart, Lung and Blood Institute
NIA-AA	The National Institute on Aging and the Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NMDA	*N*-Methyl-D-aspartate
NP	neuritic plaque
OFC	orbitofrontal cortex
OR	odds ratio
OSA	obstructive sleeping apnea
PD	proton density
PET	positron emission tomography
PiB-PET	Pittsburgh compound B positron emission tomography
PP	pulse pressure

preDIVA	Prevention of Dementia by Intensive Vascular Care
PSEN1	presenilin 1
PSEN2	presenilin 2
PSTG	posterior superior temporal gyrus
PVE	partial volume effect
PWML	periventricular white matter lesions
RAS	renin-angiotensin system
RCT	randomized controlled trial
RR	risk ratio
SBP	systolic blood pressure
SCOPE	Study on Cognition and Prognosis in the Elderly
SD	standard deviation
SMART	Secondary Manifestations of ARTerial disease
SVD	small vessel disease
SVM	support vector machine
TE	echo time
TI	inversion time
TIV	total intracranial volume
TP	temporal pole
TR	repetition time
VaD	vascular dementia
VASCOG	International Society for Vascular Behavioral and Cognitive Disorders
VCI	vascular cognitive impairment
WHO	World Health Organization
WM	white matter
WML	white matter lesions
WMS	white matter surface
^{1}H MRS	proton magnetic resonance spectroscopy

1 Introduction

Cognitive impairment is a common condition in individuals at older ages, and it can progress over time ultimately to extremely disabling dementia. Alzheimer disease (AD), the main cause of dementia, has reached epidemic proportions, being responsible for an enormous human, social, and economic burden. In 2010, 35 million persons worldwide were estimated to suffer from dementia, with the prevalence being predicted to at least double or even triple before 2040 (Prince et al., 2013). The annual worldwide cost of dementia has been estimated to be around 600 billion dollars (Wimo et al., 2013).

The 2014 G8 Dementia Summit identified dementia prevention as a major public health priority. It has been estimated that as many as half of AD/dementia cases are attributable to modifiable vascular and lifestyle-related risk factors, creating a clear window of opportunity for prevention (Barnes and Yaffe, 2011). The pathogenesis of AD has still not been fully elucidated, but it has become clear that the etiology of the sporadic form of the disease is complex and multifactorial. Several types of dementia-related pathologies (e.g. neurodegenerative, cerebrovascular) can share risk factors, and can be present simultaneously and interact with one another as the individual ages (Kivipelto et al., 2009). These aspects need to be taken into account in prevention studies.

New diagnostic criteria have shifted the focus from dementia to pre-dementia disease stages, and biomarkers (e.g. neuroimaging, laboratory) have become more important in the diagnosis of AD. This shift towards earlier disease stages has also led to an increased emphasis on the prevention of cognitive decline and dementia. Several multifactorial intervention trials have been launched during the past few years (Richard et al., 2012a).

The present thesis focuses on the effects of vascular risk factors and conditions (hypertension, overweight/obesity, hypercholesterolemia, coronary heart disease) from midlife to late-life on dementia-related structural brain changes evaluated by MRI in older aged individuals. Since Alzheimer and cerebrovascular pathologies can take a long time to develop before the onset of dementia, a life-course perspective is needed to identify risk factors. In addition, vascular factor levels can change over time, and it is not clear how different patterns of change from midlife to late-life are related to MRI findings in late-life. The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study in Finland is a population-based study with information available on vascular risk factors from midlife until as long as three decades later. The CAIDE Dementia Risk Score is a validated tool for estimating dementia risk based on a midlife profile including vascular factors (Kivipelto et al. 2006). It is important to clarify if the risk score has any relation to MRI findings in addition to its dementia prediction ability. The studies in this thesis use several methods for

MRI analysis, providing information on both neurodegenerative and cerebrovascular pathologies.

2 Review of the literature

2.1 DEMENTIA, ALZHEIMER'S DISEASE AND VASCULAR COGNITIVE IMPAIRMENT

2.1.1 Diagnostic criteria for cognitive impairment and dementia

Dementia is a syndrome primarily defined by cognitive impairment so severe that it interferes with the ability to function in everyday work and social activities. A decline from the previous level of functioning also needs to be evident, and the decline should not be explained by delirium or a major psychiatric disorder (McKhann et al., 2011). According to the fourth edition of American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (American Psychiatric Association, 1994) and the International Classification of Diseases, 10th revision (ICD-10) (World Health Organization, 1993) criteria, the essential cognitive feature of dementia is memory impairment. However, not all dementia syndromes have memory impairment as their central symptom; i.e. executive functioning, visuospatial abilities, language skills or personality can also be affected.

In the fifth edition of DSM (DSM-5) published in May 2013, the concept of dementia has been replaced with the term *major neurocognitive disorder,* and memory impairment no longer needs to be the central symptom (American Psychiatric Association, 2013). In addition, the focus is no longer on the most severe stage of impairment. *Mild neurocognitive disorder* is the diagnosis used for earlier stages of cognitive disorders. The newer criteria from the National Institute on Aging and the Alzheimer's Association (NIA-AA) workgroup (McKhann et al., 2011) also emphasize the importance of broadening the previous focus on memory impairment.

2.1.2 Diagnostic criteria for Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia. Impairment in episodic memory is a characteristic feature of AD, but there are also less common nonamnestic forms of AD, particularly visuospatial and logopenic aphasic variants. The NIA-AA work group has revised the previous 1984 AD criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 2011). Brain imaging has traditionally been performed to exclude other conditions that can cause cognitive impairment, but the new criteria emphasize the inclusive role of biomarkers (brain imaging, laboratory exams) in AD diagnosis. This is also the case in the research criteria proposed by the International Working Group (IWG) in 2007 and 2010 (Dubois et al., 2007; Dubois et al., 2010). The IWG criteria refer to medial temporal lobe atrophy (MTA) on magnetic resonance

imaging [MRI], cerebrospinal fluid [CSF] markers or positron emission tomography [PET]) markers for AD diagnosis (Dubois et al., 2007).

The transition from normal cognition to AD dementia is a slow process and many elderly individuals can be placed in between these two categories. Mild cognitive impairment (MCI) refers to cognitive impairment which is not normal for age, but does not meet criteria for dementia and does not significantly affect activities of daily living (Winblad et al., 2004). Evidence of a cognitive decline includes self and/or informant report and impairment/decline as assessed in objective cognitive tasks. The prevalence of MCI varies between 10% and 20% after the age of 65 years (Lopez et al., 2003, Petersen et al., 2010, Roberts et al., 2008), and 5-10% of the individuals with MCI progress to AD each year (Manly et al., 2008). However, the majority of people with MCI in the general population do not develop dementia, and a relatively large proportion (20-30%) have been reported to revert to normal cognitive status (Ganguli et al., 2011, Manly et al., 2008). Numerous studies have investigated the use of biomarkers (alone and in combinations) in predicting conversion from MCI to AD, but it is not entirely clear how well such markers actually perform outside of specific research settings. However, neuroimaging and some other markers have been included as diagnostic tools in the new proposed criteria for MCI due to AD (Albert et al., 2011).

2.1.3 Diagnostic criteria for vascular cognitive disorders

Vascular dementia (VaD) is the second most common type of dementia (Lobo et al., 2000). There are several different diagnostic criteria sets for VaD, with the four most commonly used being DSM-IV (American Psychiatric Association, 1994), ICD-10 (World Health Organization, 1993), the State of California Alzheimer's Disease Diagnostic and Treatment Center's (ADDTC) criteria (Chui et al., 1992) and the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (Roman et al., 1993). The NINDS-AIREN criteria are generally used in clinical trials and the following features are required for VaD: cognitive decline from previous level, impairment of memory and deficits at least in two other cognitive domains, focal neurological signs or symptoms, vascular-related changes in brain imaging, and an abrupt or fluctuating disease course. VaD is a very heterogeneous condition including both cortical lesions (multi-infarct dementia) and subcortical lesions (subcortical ischemic vascular disease, strategic infarct dementia). This means that there are variations in cognitive profile and disease patterns between patients, making it difficult to formulate comprehensive and comparable diagnostic criteria (Verhey et al., 1996). Furthermore, the VaD criteria have been suggested to be "Alzheimerized" because memory impairment occupies such a central position in almost all VaD criteria, although many patients have deficits in other cognitive domains (O'Brien et al., 2003). Vascular cognitive impairment (VCI) refers to all levels of cognitive impairment caused by cerebrovascular disease (CVD) (O'Brien et al., 2003). CVD is an umbrella term for different vascular pathologies affecting the

brain, such as stroke, small vessel disease (SVD) including white matter (WM) changes (syn. WM hyperintensities, WM lesions, leukoaraiosis), lacunar infarcts, microinfarcts and microbleeds. A new set of criteria has been recently proposed for vascular cognitive disorders in the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) statement (Sachdev et al., 2014), in an attempt to provide a coherent approach to this diverse group of disorders. These criteria are in line with the DSM-5 criteria, and take into account the developments in other cognitive disorders (e.g. AD).

2.1.4 Diagnostic criteria for cognitive impairment with multiple causality

Older individuals with cognitive impairment often have a combination of pathologies in the brain, making it difficult to determine with certainty the contribution of each pathology to the clinical syndrome. In particular, the overlap between AD and CVD has attracted more attention. The previous concept of mixed dementia is currently considered as too ambiguous and is no longer recommended. The VASCOG statement recommends that clinicians should first make a syndromal diagnosis of mild or major neurocognitive disorder, and then decide which pathology is more predominant (Sachdev et al., 2014). The proposed diagnoses are e.g. mild/major vascular cognitive disorder with AD, or AD with vascular cognitive disorder (with the level of certainty of primary cause as 'possible' and not 'probable') (Sachdev et al. 2014). DSM-5 refers to the diagnoses of major or mild neurocognitive disorder as being due to multiple etiologies (American Psychiatric Association, 2013).

2.1.5 Etiology of Alzheimer's disease

The etiology of AD is still not fully clear. Over 20 years ago the amyloid hypothesis was formulated (Hardy and Allsop, 1991), and since then it has been the strongest candidate to explain the pathogenesis of AD. The amyloid hypothesis in its earliest form suggested that amyloid beta protein (Aβ) accumulated into brain parenchyma as insoluble neuritic plaques (NP) which started a neurotoxic cascade (Hardy and Allsop, 1991). This version of the amyloid hypothesis has been revised and it is currently thought that it is the soluble oligomers of Aβ that are actually neurotoxic (Hardy and Selkoe, 2002). Aβ oligomers are believed to disrupt neuronal synapse function, leading to neuronal damage and to the appearance of intracellular aggregations of hyperphosphorylated tau protein (neurofibrillary tangles, NFT). The elevated intracellular NFT formation leads to widespread neuronal damage and brain atrophy, and ultimately to clinical dementia (Hardy and Selkoe, 2002). Although the amyloid hypothesis is widely supported, it has raised many questions and criticisms (Drachman, 2014, de la Torre, 2004, Hardy and Selkoe, 2002). High intracerebral concentrations of Aβ have been shown to decrease memory and synaptic plasticity in rodents (Puzzo and Arancio, 2013), but interestingly picomolar concentrations have been reported to have beneficial effects (Puzzo et al., 2008). In fact, the physiological functions of Aβ are still poorly understood with some of the

partly unresolved questions being: Are amyloid and its oligomers as neurotoxic for human neurons as previously thought? Why can some elderly people have a notable amount of neuritic plaques at autopsy, but have displayed no cognitive impairment? Why have immunotherapies focusing on clearance of insoluble Aβ failed to improve cognition? It is possible that the amyloid hypothesis alone may not be enough, and AD should be considered more as a syndrome where multiple factors such as vascular pathology or inflammation exert additional influences.

Tau pathology is thought to progress in phases and the brain atrophy in AD tends to follow the same structural pattern (Braak and Braak, 1995, Whitwell et al., 2008). Aβ depositions measured by Pittsburgh compound B positron emission tomography (PiB-PET) also showed correlation with brain atrophy (Bourgeat et al., 2010, Dore et al., 2013). Interestingly, the rate of brain atrophy in antemortem MRI did not correlate with Aβ burden measured by immunohistology in post-mortem autopsy samples (Josephs et al., 2008). In familial AD, structural brain changes are encountered decade(s) before the appearance of any clinical symptoms (Bateman et al., 2012, Fox, 2012, Reiman et al., 2012), but brain atrophy preceding sporadic AD probably starts later (Jack et al., 2004, Jack et al., 2010, Jagust et al., 2006). Atrophy as well as the preceding tau pathology starts from the medial temporal lobe structures, initially affecting the entorhinal cortex, later progressing to other parts of the limbic system, and finally involving the neocortex (Liang et al., 2013). This is the case in the typical late-onset AD, but in the early-onset AD, medial temporal lobe structures are often preserved and atrophy is observed in the parietal lobes instead (Karas et al., 2007). Other more uncommon disease progression patterns have also been reported (Whitwell et al., 2012). In the final stages of AD, brain atrophy is extremely diffuse and extending over the whole cerebral cortex and also involving subcortical structures.

2.1.6 Etiology of vascular cognitive disorders

WM lesions (WML) are a characteristic feature of vascular cognitive impairment caused by SVD. WML appear as hyperintensities in cerebral WM on T2-weighted MRI, and are generally classified as periventricular or subcortical based on their location (Figure 1). WML are a very common finding in the general population. About 70-88% of people aged 50-65 years have some degree of WML, and around 20% of people older than 65 years exhibit severe changes (Launer, 2004). The most often seen WML are age-related and are particularly strongly associated with hypertension. The loss of smooth muscle cells from the tunica media, narrowing of the lumen due to fibro-hyaline deposits (i.e. *hyalinosis*) and atheromas, and thickening of the vessel wall are the main characteristics of this arteriolosclerosis-type of WML. These changes are thought to impair autoregulation, leading to tissue hypoperfusion and finally to ischemia and demyelination (Pantoni, 2010). Increased oxygen extraction is also seen in the areas of WML, supporting their ischemic origin (Kalaria et al., 2012). In addition, blood-brain barrier damage, local subclinical

inflammation, oligodendrocyte apoptosis, and cerebral amyloid angiopathy (CAA) have been postulated to have a role in the pathogenesis of WML (Pantoni, 2010).

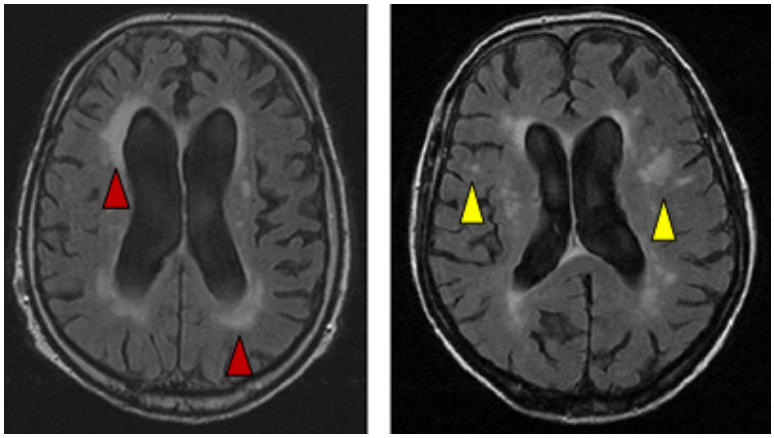


Figure 1. WML on T2-weighted FLAIR MRI. Red arrows point periventricular WML and yellow arrows subcortical WML.

Microbleeds are small hemorrhages inside the brain parenchyma. They can be seen at autopsy or in MRI if the appropriate MR sequence (such as gradient-echo) is used. CAA is often seen in AD and it predisposes the blood vessels to hemorrhaging. Lacunar infarcts are small infarcts usually situated deep in subcortical WM or GM nuclei. They are caused by occlusion of perforating arteries and hypertension is thought to be the main risk factor (Roman et al., 2002). Symptoms vary depending on the location and amount of lacunes. In addition, cortical microinfarcts in vascular watershed areas may be seen as a consequence of cerebral hypoperfusion (Suter et al., 2002).

SVD is associated with a cognitive impairment (Pantoni et al., 2007) and increased risk of dementia (Savva et al., 2009). In contrast to AD, a deficit in episodic memory is not always present, and impairment in executive functioning can often be seen (Gunning-Dixon and Raz, 2000). Mood (O'Brien et al., 1998), gait (Baezner et al., 2008, Baloh et al., 2003) and urinary (Poggesi et al., 2008) problems are also present in SVD. SVD-related problems may be more difficult to diagnose with criteria focusing on memory impairment. In addition, the diagnostic criteria for VaD have been heterogeneous and designed primarily for detecting large-vessel disease (Wiederkehr et al., 2008). The importance of mild SVD in midlife is still unclear, because not all lesions are associated with cognitive and functional disabilities. The location of WML may also be important, e.g. periventricular WML have been suggested to exert a greater negative impact on cognition than subcortical lesions (Bolandzadeh et al., 2012). However, clinically silent SVD may signal an increased vascular risk profile and the need for better risk factors control.

WML often co-exist with AD-type pathology (Pantoni et al., 2009) and brain atrophy (Appelman et al., 2009), which has initiated a debate about the role of WML in AD. Vascular lesions can lower the threshold for AD pathology to cause clinical symptoms in elderly people (Schneider et al., 2007, Snowdon et al., 1997, Toledo et al., 2013). In addition, animal experiments suggest that Aβ deposition in the vessel wall can disrupt the normal function of endothelial cells, exposing the brain to ischemic injury (Iadecola, 2003). Many people with an AD diagnosis have a mixture of both AD- and vascular-type pathologies, and 'pure' AD may be less common than previously thought (Kivipelto et al., 2009, Neuropathology Group. Medical Research Council Cognitive Function and Aging Study, 2001).

2.1.7 Brief overview of risk factors for cognitive impairment and dementia

Older age (Ritchie and Kildea, 1995), female sex (Fratiglioni et al., 2000) and family history (van Duijn et al., 1991) are established risk factors for AD. The effects of genes are more pronounced in forms of AD with onsets before the age of 65 years (i.e. early-onset AD). Familial AD is often characterised by mutations in three genes: amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) (Tanzi and Bertram, 2001). However, these familial forms of AD are very rare, affecting only 1-2% of AD cases. Apolipoprotein E (ApoE) has an important role in cholesterol metabolism, and the ε4 allele of the apolipoprotein E gene (APOE ε4) has been linked with an elevated risk of sporadic AD. It has been estimated that APOE ε4 accounts for about 60% of the genetic component of sporadic AD (Rubinsztein and Easton, 1999). A variety of other genes have been proposed as risk factors for AD (www.alzgene.org).

It has been suggested that there are several modifiable risk factors for AD, in particular there is stronger epidemiological evidence for midlife hypertension, hypercholesterolemia, obesity, smoking, diabetes and cardiac diseases (Polidori et al., 2012). Other proposed risk factors are physical inactivity, unhealthy diet, high alcohol intake, depression and traumatic brain injury (Solomon et al., 2014). In contrast, a high level of education, a physically, socially and mentally active lifestyle, moderate alcohol consumption, and healthy diet (e.g. Mediterranean diet) have been postulated to have protective effects against dementia (Solomon et al., 2014).

2.2 VASCULAR RISK FACTORS AND THE AGING BRAIN

2.2.1 Blood pressure and dementia

A low BP at older ages was associated with an increased risk of AD in earlier cross-sectional studies (Guo et al., 1996, Landin et al., 1993). Subsequently, several large longitudinal studies showed that high BP in midlife increased the risk of AD/dementia after 20-30 years (Kivipelto et al., 2001b, Launer et al., 2000). It has also been reported that BP levels actually decrease when the disease progresses (Burke et al., 1994). The decline in BP seems to start at least three years before diagnosis (Qiu

et al., 2004), possibly even earlier (Skoog et al., 1996). The decrease in BP begins earlier particularly in individuals with cardiovascular disorders (Qiu et al., 2004).

2.2.2 Blood pressure regulation

The brain is an important part of the complex system regulating BP. The role of kidneys and the adrenal glands in BP regulation through the renin-angiotensin system (RAS) is well recognized (Herichova and Szantoova, 2013), but specific brain regions are also involved in BP regulation. Many brainstem nuclei regulate vascular tone through the autonomic nervous system, and the brainstem is itself controlled by subcortical structures such as thalamus (Dampney et al., 2003). The hypothalamus synthetises anti-diuretic hormone (ADH) which regulates blood osmolality and sodium levels, which also have an impact on BP levels (Jennings and Zanstra, 2009).

Data from animal and human studies indicate that BP is also regulated by cortical modulation. The network consisting of the insular cortex, anterior cingulate gyrus and amygdala has an important impact on the central autonomic nervous system (Nagai et al., 2010). Insular cortex damage has been associated with BP fluctuations, arrhythmia, myocardial injury and baroreceptor sensitivity (Nagai et al., 2010), and stimulation of the insular cortex can cause changes in heart rate and BP in humans (Oppenheimer et al., 1992). In *in vivo* studies, the left insular cortex seemed to be involved in regulating the parasympathetic tone of the cardiovascular system, while the right insular cortex was more extensively involved in regulating sympathetic tone (Oppenheimer et al., 1992). This central nervous system network has been referred to as the "Brain-Heart Axis" (Nagai et al., 2010).

2.2.3 The brain as a target organ for hypertension

Brain tissue is greatly dependent on the vasculature. Systemic arterial BP levels vary during the day, but autoregulation of brain arterioles ensures an appropriate cerebral blood flow (CBF) (Strandgaard, 1976). Chronic hypertension can contribute to arteriosclerosis, with stiffening and thickening of the arteriole walls and dysfunctional autoregulation. The affected vessels cannot adequately adjust their lumen according to BP level fluctuations, leading to hypoperfusion and tissue hypoxia (Feldstein, 2012). It seems that autoregulation is relatively well preserved with BP values lower than 160/90 mmHg (Serrador et al., 2005), but hypertension higher than 160/90 mmHg has been postulated as being harmful (Immink et al., 2004). Studies in elderly hypertensive individuals detected decreased values of regional CBF in the frontal lobe, cingulate cortex and hippocampus, indicative of cerebral hypoperfusion in these areas (Beason-Held et al., 2007, Dai et al., 2008). Interestingly, cerebral hypoperfusion has also been linked to incident dementia in a large prospective study (Ruitenberg et al., 2005).

Results from autopsy studies suggest that long-term hypertension is associated with an increased accumulation of Alzheimer pathology. A large study of twins with a 40 year follow-up time showed increased neocortical and hippocampal NP deposition in subjects with high midlife systolic BP (SBP) (Petrovitch et al., 2000). In

the same study, individuals with high midlife diastolic BP (DBP) levels had more hippocampal NFT compared to controls. Midlife elevated DBP has also been related to decreased plasma Aβ levels 15 years before AD diagnosis (Shah et al., 2012). There are several hypotheses concerning the mechanisms by which hypertension may affect AD pathology, e.g. tissue hypoxia, microinfarctions, inflammation or oxidative stress (Feldstein, 2012). In addition, AD pathology can affect the cerebral vasculature. Aβ deposition in brain artery walls causes CAA, leading to vessel wall rupture, hemorrhages and infarctions (Thal et al., 2008). Furthermore, capillary CAA may develop slowly, occluding the vessel lumen, impairing blood flow and causing hypoperfusion in the respective vasculature areas (Thal et al., 2008). Aβ is also believed to attenuate endothelium-mediated dilatation as a response to somatosensory activation, predisposing the brain tissue to hypoperfusion (Niwa et al., 2000).

The mechanisms underlying the pattern of decline in BP over time observed in people who later on develop dementia are not yet clear. One possible explanation could be pathological changes/atrophy in brain regions involved in BP regulation. Cholinergic neurons stimulate regional blood flow, and atrophy of these neurons may disturb normal vessel functioning (Staessen et al., 2007). The NFT burden has consistently been related to brain volumes (Gosche et al., 2002, Josephs et al., 2008, Nagy et al., 1996, Silbert et al., 2003). NFT pathology reaches the insular cortex already in the pre-clinical phase of AD (Braak et al., 1998), and the insula has an important role in BP regulation.

Midlife hypertension has been related to WML in several epidemiological studies (Table 1), and WML have been associated with cerebral atrophy (Appelman et al., 2009). It is possible that WM changes can affect GM integrity, and vice versa. One hypothesis involves Wallerian degeneration (Waller, 1850) in this process. However, considering discrepancies between the severity of changes in adjacent cortical and WM areas, and the absence of histological markers of Wallerian degeneration in affected WM (Pantoni and Garcia, 1997), the relevance of Wallerian degeneration in the development of WM changes is still unclear.

2.2.4 Blood pressure and structural brain changes

One of the earliest studies investigating the relation between hypertension and brain volumes was published in 1984 (Hatazawa et al., 1984). In this cross-sectional study, hypertensive subjects had a smaller ratio of brain matter volume to intracranial volume, indicative of brain atrophy. Since then many studies focusing on BP and brain volumes have been published. Many of these studies have been cross-sectional or had short follow-up times, which did not allow any assessment of the long-term effects of BP, or of potential reverse causality.

Results from cross-sectional studies using different MRI analysis methods indicate that the temporal and frontal lobes are particularly vulnerable to the detrimental effects of hypertension. Findings vary concerning which structures of medial and frontal lobes are affected, but they have been more consistent for a few areas:

superior frontal gyrus (Chen et al., 2006, Gianaros et al., 2006, Leritz et al., 2011), medial frontal gyrus (Chen et al., 2006, Leritz et al., 2011, Taki et al., 2008), prefrontal cortex (Raz et al., 2003, Raz et al., 2007), inferior temporal gyrus (Raz et al., 2007, Taki et al., 2008) and superior temporal gyrus (Chen et al., 2006, Leritz et al., 2011). Altogether 14 longitudinal studies on BP and brain volumes with follow-up times ranging from 2 to 36 years have been published (Table 1). Both elevated midlife SBP and DBP have been linked with total brain volume loss in late-life (DeCarli et al., 1999a, Heijer et al., 2003, Petrovitch et al., 2000, Swan et al., 1998). This association is supported by many cross-sectional studies (Goldstein et al., 2002, Hatazawa et al., 1984, Manolio et al., 1994, Nagai et al., 2008, Salerno et al., 1992, Schmidt et al., 2004, Strassburger et al., 1997), but not all (Enzinger et al., 2005, Korf et al., 2007, Skoog et al., 1998). The inconsistencies between reports may be explained by differences in study populations and methods (e.g. it can take time for hypertension to affect total brain volume), or by reverse causality (i.e. already present brain pathology affecting BP).

Elevated BP has been linked to a reduced hippocampal volume in three longitudinal studies using manual tracing (den Heijer et al., 2005b, Korf et al., 2004, Raz et al., 2005). In a study with a 25 year follow-up time, individuals with high values of midlife SBP and DBP had reduced hippocampal volumes in late-life (Korf et al., 2004). Low amygdala volume (den Heijer et al., 2005b) and low orbitofrontal cortex volume (Raz et al., 2005) have also been associated with high BP, but other areas such as insular cortex have not been investigated in longitudinal studies.

The effects of midlife BP on late-life WML have been assessed in two longitudinal studies with follow-up times of around 20 years (Table 1). In a study investigating twin males, midlife hypertension was related to WML as assessed with MRI 25 years later (Carmelli et al., 1999, DeCarli et al., 1999a, Swan et al., 1998). The strengths of this study are a large cohort and long follow-up time, but the focus on a twin male population makes it difficult to generalize results. The Rotterdam Scan Study, a longitudinal population-based study including over 1000 subjects (514 with nearly 20 years follow-up time), also reported an association between midlife hypertension and late-life WML (de Leeuw et al., 1999). In Rotterdam Scan Study, also a J-shape relationship was observed between changes in DBP and WML.

Longitudinal studies with shorter follow-up times (two to five years) have reported an association between baseline hypertension and WML progression (Firbank et al., 2007, Raz et al., 2007, Schmidt et al., 1999, Verhaaren et al., 2013). Interestingly, a diffusion tensor imaging (DTI) study showed WM injury in hypertensive (SBP $\geq$ 140 and/or DBP $\geq$ 100) individuals younger than 40 years (Maillard et al., 2012). It is difficult to draw clear conclusions concerning the importance of SBP versus DBP, because findings from various studies are inconsistent (Table 1). Variations between different studies can also be seen concerning the relationships of SBP or DBP with brain GM volumes (Table 1) (Beauchet et al., 2013).

Table 1. Summary of longitudinal studies focusing on blood pressure and brain GM structures, total brain volume and WML

Study	**Population characteristics**	**Method**	**Outcome**	**Covariates**	**Main results**
Swan et al. 1998 (NHLBI study, USA)	N=392 Cognitive status not provided All twin men Mean baseline age: 47 y Mean follow-up time: 26 y	1.5 T MRI Semi-automatic segmentation	Brain and WML volume	Age, education, baseline neurobehavioral performance, presence of CVD at late-life	High midlife SBP was associated with lower brain volume and increased WML volume in late-life.
Carmelli et al. 1999 (NHLBI study, USA)	N=74 Cognitive status not provided All twin men Mean baseline age: 48 y Mean follow-up time: 25 y	1.5 T MRI Semi-automatic segmentation	Brain and WML volume	-	High midlife SBP and DBP were associated with WML later in life. Late-life high SBP was associated lower brain volume.
DeCarli et al. 1999a (NHLBI study, USA)	N=414 Cognitive status not provided All twin men Mean baseline age: 47 y Mean follow-up time: 26 y	1.5 T MRI Semi-automatic segmentation	Brain and WML volume	-	Midlife high DBP (and less strongly high SBP) was associated with lower brain and increased WML volume in late-life.
de Leeuw et al. 1999 (Rotterdam Scan Study, Netherlands)	N=1077 No dementia Mean baseline age: 51 y Mean follow-up time: 20 y	1.5 T MRI Visual rating	WML	Age, sex, BMI, cholesterol, smoking, diabetes	Increased midlife SBP and DBP were associated with late-life WML. J-shape association was found between DBP change and WML.
Meyer et al. 1999 (USA)	N=224 No dementia Mean baseline age: 60 y Mean follow-up time: 4 y	Xenon-enhanced CT Manual tracing	Brain atrophy, perfusion and leukoaraiosis	Age	High BP was associated with cerebral atrophy and leukoaraiosis.
Schmidt et al. 1999 (ASP study, Austria)	N=273 No dementia Mean baseline age: 60 y Mean follow-up time: 3 y	1.5 T MRI Visual rating	WML progression	Age, sex	High baseline DBP was associated with WML progression.

continues

Table 1. (continued)

Study	Population characteristics	Method	Outcome	Covariates	Main results
Petrovitch et al. 2000 (HAAS study, USA)	N=243 Dementia included All men Mean baseline age: ~50 y Mean follow-up time: 36 y	Neuropathological assessment at autopsy	NP, NFT, brain weight	All models: age, APOE, BP treatment Brain weight model: in addition height, BMI, presence of cerebrovascular lesions	High SBP was associated with lower brain weight. High SBP was associated also with neocortical and hippocampal NPs accumulation and high DBP with hippocampal NFTs.
Dufouil et al. 2001 (EVA MRI cohort, France)	N=845 Cognitive status not provided Mean baseline age: 65 y Mean follow-up time: 4 y	1.0 T MRI Visual rating	WML	Age, sex, history of vascular disease	Baseline hypertension was associated with increased WML in follow-up.
Heijer et al. 2003 (Rotterdam Scan Study, Netherlands)	N=513 No dementia Mean baseline age: 51 y Mean follow-up time: 21 y	1.5 T MRI Visual semi-quantitative rating	Cortical atrophy	Age, sex, smoking, diabetes, BMI, WML, antihypertensive treatment	High DBP in midlife and high and low DBP in late-life were associated with cortical atrophy. Also steep decline in DBP from midlife to late-life was associated with cortical atrophy.
Korf et al. 2004 (HAAS study, USA)	N=543 Dementia included All twin men Mean baseline age: ~55 y Mean follow-up time: ~25y	1.5 T MRI Manual tracing	Hippocampal volume	Age, education, APOE, dementia, smoking, alcohol, WML, lacune infarcts, subcortical and cortical infarcts	High midlife SBP and DBP were associated with hippocampal atrophy in late-life in men without antihypertensive treatment.
Wiseman et al. 2004 (SCOPE study, UK)	N=154 No dementia Mean baseline age: ~77 y Mean follow-up time: 1.5 y	1.5 T MRI Semi-automatic segmentation (whole brain), manual tracing (hippocampus) and visual rating (WML)	Brain and hippocampus volume, WML	Age, sex, TIV	High BP was associated with lower total brain volume and increased WML.

continues

Table 1. (continued)

Study	Population characteristics	Method	Outcome	Covariates	Main results
Den Heijer et al. 2005b (Rotterdam Scan Study, Netherlands)	N=511 No dementia Mean baseline age: 69 y Mean follow-up time: 5 y	1.5 T MRI Manual tracing	Hippocampus and amygdale volume	Age, sex, additional cardiovascular factors (BP, BMI, smoking, cholesterol), antihypertensive treatment	High untreated DBP in baseline was associated with smaller hippocampal volume; low treated DBP in follow-up was associated with low amygdale volume.
Enzinger et al. 2005 (ASPS study, Austria)	N=201 No dementia Mean baseline age: 60 y Mean follow-up time: 6 y	1.5 T MRI Automatic segmentation	Brain atrophy	Age, HbA1C, BMI, alcohol, APOE	BP was not associated with brain atrophy.
Goldstein et al. 2005 (USA)	N=155 No dementia Mean baseline age: 66 y Mean follow-up time: 5 y	1.5 T MRI Manual tracing	Total brain atrophy, WML	Age, sex, BMI, activity	BP sleep variability was associated with total brain atrophy, WML and insular subcortical hyperintensities.
Raz et al. 2005 (USA)	N=72 No dementia Mean baseline age: 53 y Mean follow-up time: 5 y	1.5 T MRI Manual tracing	Regional brain atrophy	-	High BP was associated with orbitofrontal cortex and hippocampal atrophy (and also with prefrontal WM atrophy).
Firbank et al. 2007 (SCOPE study, UK)	N=163 No dementia Mean baseline age: 77 y Mean follow-up time: 2 y	1.5 T MRI Automatic (WML) and semi-automatic (brain atrophy) segmentation	Rate of cerebral atrophy and WML volume increase	Age, sex, smoking, hyperglycemia, hypercholesterolemia, antihypertensive treatment	High SBP was associated with increased brain atrophy rate, and high DBP with WML volume in late-life.
Raz et al. 2007 (USA)	N=46 No dementia Mean baseline age: 61 y Mean follow-up time: 5 y	1.5 T MRI Manual tracing	Cerebral atrophy in 12 areas and WML volume progression	Age, sex, education	High BP was associated with cortical atrophy in posterior regions and increase in WML volume.

continues

Table 1. (continued)

Study	Population characteristics	Method	Outcome	Covariates	Main results
Vlek et al. 2009 (SMART-MR study, Netherlands)	N=331 Vascular disease Mean baseline age: 58 y Mean follow-up time: 4 y	1.5 T MRI Automatic segmentation	Progression of cerebral atrophy and lacunar infarcts	Age, sex, diabetes, WML volume, antihypertensive treatment, TIV	High BP was not associated with cerebral atrophy in people with severe vascular disease (but incidence of lacunar infarcts was higher).
Debette et al. 2011 (Framingham Offspring Study, USA)	N=1352 No dementia Mean baseline age: 54 y Mean follow-up time: 6 y	1.0 and 1.5 T MRI Semi-automatic segmentation	Change in total brain volume, temporal horn volume and WML volume	Sex, age, follow-up time, baseline brain measurements	Midlife hypertension was associated with accelerated WML progression.
Godin et al. 2011 (Three-City Dijon MRI study, France)	N=1319 Dementia included Mean baseline age: 68 y Mean follow-up time: 4 y	1.5 T MRI Automatic segmentation	WML volume	Age, sex, TIV, diabetes, education, cardiovascular disease, antihypertensive treatment	Increase in baseline DBP predicted WML progression. Initiation of antihypertensive medication decreased the progression of WML in subjects with SBP over 160 mmHg at baseline.
den Heijer et al. 2012 (Rotterdam Scan Study, Netherlands)	N=301 No dementia Mean baseline age: 72 y Mean follow-up time: 10 y	1.5 T MRI Automatic segmentation	Hippocampal atrophy	Age, sex	Baseline DBP under 70 mmHg or over 90 mmHg was associated with increased hippocampal atrophy.
Jochemsen et al. 2013 (SMART-MR study, Netherlands)	N=663 Vascular disease Mean baseline age: 57 y Mean follow-up time: 4 y	1.5 T MRI Automatic segmentation	Brain atrophy, WML volume progression	Age, sex, follow-up time, baseline brain volume, smoking, alcohol, BMI, DM, hyperlipidemia, carotid atherosclerosis, arterial disease category, antihypertensive treatment, WML, brain infarcts	Low baseline DBP and declining DBP predicted increase in ventricular fraction (subcortical atrophy).

continues

Table 1. (continued)

Study	**Population characteristics**	**Method**	**Outcome**	**Covariates**	**Main results**
Verhaaren et al. 2013 (Rotterdam Scan Study, Netherlands)	N=665 No dementia Mean baseline age: 62 y Mean follow-up time: 4 y	1.5 T MRI Automatic segmentation	WML volume progression	Age, sex, TIV, antihypertensive treatment, cholesterol, BMI, alcohol, smoking, diabetes	Baseline high SBP and DBP were associated with increased WML volume progression. Hypertension treatment seemed to slow WML progression.

2.2.5 Adiposity and dementia

Midlife adiposity (i.e. overweight, obesity) has been associated with an increased risk of dementia in longitudinal population-based studies (Kivipelto et al., 2005, Whitmer et al., 2005a). As with BP, the association seems to depend on age and a lower BMI was linked to dementia at older ages (Atti et al., 2008, Nourhashemi et al., 2003). Loss of weight a few years before AD diagnosis is thought to be a marker of incipient dementia rather than a risk factor for AD (Gustafson, 2012).

Several mechanisms may explain the association between adiposity and AD, e.g. vascular factors, hyperinsulinemia, advanced glycocylation products, adipokines, cytokines and leptins produced by adipose tissue (Luchsinger and Gustafson, 2009). Adipose tissue is hormonally very active, and inflammation-related adipokines as well as dietary regulation-related leptins have been associated with AD and brain GM volumes (Gustafson, 2012, Rajagopalan et al., 2013). However, these mechanisms are still not entirely clear (Luchsinger and Gustafson, 2009).

2.2.6 Adiposity and structural brain changes

Low BMI at older ages and a declining BMI over time have been associated with AD neuropathology (Aβ and NFT) at brain autopsy as well as with CSF markers and PiB-PET-imaging (Buchman et al., 2006, Vidoni et al., 2011). This is in line with findings from epidemiological studies concerning late-life BMI and AD risk. In addition, elevated BMI during 24 years follow-up in elderly people was associated with lower temporal lobe volume as measured with computerized tomography (CT) in late-life (Gustafson et al., 2004a). Increased BMI values were related to lower total GM volume in otherwise healthy middle-aged postmenopausal women (Soreca et al., 2009). Similar results have been reported in studies with shorter follow-up times (Bobb et al., 2012, Driscoll et al., 2012, Enzinger et al., 2005). Increased BMI has also been associated with cortical thinning in a cognitively healthy middle-aged Norwegian population after an average follow-up of 3.6 years (Walhovd et al., 2013).

The extent WML have been linked with adiposity in one longitudinal Swedish study (Gustafson et al., 2004b). In a sample of 70 years old women followed-up for 18 years, CT scans were performed at the age of 85-88 years. Every 1.0 increase in BMI at the age of 70 doubled the risk of WML later on. Several cross-sectional studies investigating WM integrity as assessed with either DTI or proton magnetic resonance spectroscopy (^{1}H MRS) support this finding (Gazdzinski et al., 2008, Mueller et al., 2011, Stanek et al., 2011, Verstynen et al., 2012). A recent Japanese cross-sectional study investigating 35-74 years old (mean 55.3 years) office workers without any prior cerebrovascular disease linked increased visceral fat accumulation with WML and lacunar infarcts. Interestingly, no association was found between high BMI and WML or lacunes, suggesting that it was visceral fat accumulation rather than general obesity and subcutaneous fat accumulation which seemed to be more harmful for cerebral white matter (Yamashiro et al., 2014).

2.2.7 Cholesterol and dementia

Elevated total cholesterol in midlife has been linked to increased risk of AD/dementia in longitudinal studies (Kivipelto et al., 2001b, Whitmer et al., 2005b). Studies with shorter follow-up times and older populations have reported conflicting results. Similarly to BP and BMI, total cholesterol levels seem to decline over time in individuals who susequently develop dementia (Solomon et al., 2007).

Midlife total cholesterol levels have been related to accumulation of Aβ and NFT in autopsy studies (Launer et al., 2001). In addition, animal studies have revealed accumulation of Aβ and NFT in animals with cholesterol-rich diet (Rahman et al., 2005, Sparks et al., 1994). In middle-aged people, higher total cholesterol levels were associated with glucose hypometabolism in brain regions relevant for AD (Reiman et al., 2010). Cholesterol has an important role in atherosclerosis, and vascular pathology may partly explain the association with AD/dementia. Other mechanisms may involve oxysterols, cholesterol metabolites which can pass through the blood-brain barrier and function as a link between the circulating and brain cholesterol pools (Björkhem et al., 2009).

2.2.8 Cholesterol and structural brain changes

Results on the association of cholesterol with structural brain changes are inconsistent. Low high density lipoprotein (HDL) was associated with reduced hippocampal volume (Wolf et al., 2004), but a larger study including subjects without dementia did not confirm this finding (den Heijer et al., 2005a). A large cross-sectional Swedish study revealed that men with hypercholesterolemia had smaller volumes of hippocampal and entorhinal cortex as compared to controls (Qiu et al., 2012), but this association was not detected in other studies (Koschack et al., 2009, Wolf et al., 2004). Surprisingly, increasing cholesterol levels were linked with thicker cortex across the whole brain in one cross-sectional study including subjects with no history of cerebrovascular or neurological diseases (Leritz et al., 2011). Low midlife HDL levels were associated with higher WML load at late-life, but no association was seen for low density lipoprotein (LDL) or total cholesterol and WML (Carmelli et al., 1999). The role of cholesterol in dementia-related diseases is difficult to evaluate because peripheral and brain cholesterol metabolism are separated by the blood-brain barrier, and the links between the two cholesterol pools are not entirely clarified (Björkhem et al., 2009).

2.3 HEART DISEASES AND THE AGING BRAIN

2.3.1 Heart diseases and dementia

Coronary heart disease (CHD) has been associated with dementia in several longitudinal studies (Aronson et al., 1990, Brayne et al., 1998, Ross et al., 1999), but findings with regard to AD specifically are less consistent (Brayne et al., 1998, Hayden et al., 2006). Autopsy studies have shown increased accumulation of AD neuropathology in individuals with CHD and without dementia (Sparks et al., 1990),

and this association was even stronger in APOE ε4 carriers (Beeri et al., 2006). Having CHD in midlife increased the risk of poorer cognitive functioning in a study with an 11 year follow-up time (Singh-Manoux et al., 2003), but this finding was not supported by other epidemiological studies (Bursi et al., 2006, Grubb et al., 2000). Similar to the situation with CHD, heart failure (HF) (Qiu et al., 2006) and atrial fibrillation (AF) (Bunch et al., 2010, Miyasaka et al., 2007) have also been linked with cognitive impairment, although with inconsistent findings (Marengoni et al., 2011, Peters et al., 2009). AF is a major risk factor for stroke, but an independent association between AF and AD/dementia has also been reported (Bunch et al., 2010, Miyasaka et al., 2007, Ott et al., 1997).

2.3.2 Coronary heart disease and structural brain changes

Several cross-sectional studies have focused on CHD and brain GM or WM changes (Table 2), but so far no longitudinal studies have taken disease duration into account. CHD was associated with decreased brain volume in a population of twin veterans in USA, with the association being more pronounced among APOE ε4 carriers (DeCarli et al., 1999b). A Dutch study reported decreased hippocampal volume in subjects with CHD in a small sample of middle-aged participants, but no differences were found in total brain volume (Koschack and Irle, 2005). Interestingly, regions associated with AD such as temporal lobe, posterior cingulate and precuneus had lower volumes in individuals with prior myocardial infarction in a small study including 18 non-demented subjects (Almeida et al., 2008). CHD was not related to structural brain changes (visual rating of ventricular enlargement, sulcal widening and WML) in the Cardiovascular Health Study (Manolio et al., 1994). Measures of atherosclerosis such as coronary artery calcification (CAC) and internal carotid artery calcification, were associated with WML in several studies, and this association was independent of several vascular risk factors (Table 2). The larger AGES-Reykjavik study also reported associations between CAC and brain GM and WM volumes (Vidal et al., 2010). Furthermore, a study using ^{1}H MRS detected impaired WM integrity already in midlife in people with subclinical atherosclerosis (Haley et al., 2010).

Table 2. Summary of cross-sectional studies focusing on CHD/atherosclerosis and structural brain changes

Study	**Population characteristics**	**Method**	**Outcome**	**Covariates**	**Main results**
Bots et.al 1993 (Rotterdam study, Netherlands)	N=111 Cognitive status not provided Mean age: 75 y	1.5 T MRI Visual rating	WML	Age, sex, hypertension, total cholesterol, HDL, smoking	Carotid artery intima media thickness was positively associated with WML. A trend was seen for myocardial infarction and WML.
Manolio et al. 1994 (CHS study, USA)	N=303 Cognitive status not provided Age: over 65 y	1.5 T MRI Visual rating	Ventricular enlargement, sulcal widening, WML	-	CHD was not associated with MRI changes.
DeCarli et al. 1999 (NHLBI study, USA)	N=396 Cognitive status not provided Mean age: 72y	1.5 T MRI Semi-automatic segmentation	Parenchyma and intracranial fluid volume WML volume	Age, education, head size	CHD was associated with decreased brain parenchyma volume, particularly in APOE4 carriers.
Koschack et al. 2005 (Germany)	N=40 No dementia All men Mean age: 59 y	1.5 T MRI Manual tracing (hippocampus) Automatic segmentation (brain volumes) Visual rating (WML)	Hippocampal and brain volumes, WML	Age, education, ICV, BP, BMI, fasting glucose, cholesterol	CHD was associated with decreased hippocampal volume.
Rosano et al. 2005 (CHS study, USA)	N=409 Dementia included Mean age: 79 y	1.5 T MRI Visual rating	WML, ventricular enlargement, brain infarcts	Age, sex, race, cardiovascular disease	High CAC was associated with more severe WML and brain infarcts and there was a trend towards ventricular enlargement.

continues

Table 2. (continued)

Study	Population characteristics	Method	Outcome	Covariates	Main results
Almeida et al. 2008 (Australia)	N=18 No dementia Mean age: 70 y	1.5 T MRI Automatic segmentation	Brain volumes	Age, sex, handedness, total brain volume	Prior myocardial infarction was associated with a loss of GM volume in the left medial frontal lobe, precentral and postcentral cortex, right temporal lobe, left middle temporal gyrus, left precuneus and posterior cingulate.
Ikram et al. 2008 (Rotterdam Scan Study, Netherlands)	N=436 Dementia included Mean age: 73 y	1.5 T MRI Automatic segmentation (WML volume) Visual rating (infarct)	WML volume, brain infarcts	Age, sex, smoking, BP, cholesterol, diabetes, AF, carotid intima media thickness, cardiovascular drugs	Unrecognised myocardial infarction was associated with greater WML volume and increased amount of brain infarcts.
Geerlings et al. 2010 (SMART-MR study, Netherlands)	N=1044 Cognitive status not provided Mean age: 58 y	1.5 T MRI Automatic segmentation (brain volumes and WML) Visual rating (infarcts)	Brain and WML volumes, brain infarcts	Age, sex	Atherosclerosis did not seem to affect brain atrophy rate. WML and silent brain infarcts were more common in the group with atherosclerosis.
Vidal et al. 2010 (AGES-Reykjavik study, Iceland)	N=4250 Dementia included Mean age: 76 y	1.5 T MRI Automatic segmentation (brain and WML volumes) Visual rating (infarcts and microbleeds)	Brain and WML volumes, brain infarcts and microbleeds	Age, sex, ICV, education, smoking, CHD, hypertension, diabetes, midlife SBP, cholesterol	High CAC was associated with more severe WML, infarcts and microbleeds as well as with lower gray, white and total brain matter volume.

continues

Table 2. (continued)

Study	Population characteristics	Method	Outcome	Covariates	Main results
Bos et al. 2011 (Rotterdam study, Netherlands)	N=885 Cognitive status not provided Mean age: 67 y	1.5 T MRI Automatic segmentation (WML volume) Visual rating (microbleeds and infarcts)	WML volume, microbleeds and cerebral infarcts	Age, sex, ICV, BMI, BP, diabetes, cholesterol, smoking, cardiovascular drugs, ultrasound-based carotid plaque score	Coronary, aortic arch, extracranial and intracranial carotid artery calcification was associated with increased WML volume and brain infarcts.
Kim et al. 2011 (Republic of Korea)	N=312 No dementia Mean age: 69 y	1.5 T MRI Visual rating	WML, microbleeds and lacunar infarcts	Age, sex, hypertension, diabetes, hypercholesterolemia, smoking, CRP	CAC severity was associated with WML, cerebral microbleeds and lacunar infarcts.
Almeida et al. 2012 (Australia)	N=155 No dementia Mean age: 68 y	1.5 T MRI Automatic segmentation	Regional brain volumes	Age, sex, homocysteine (covariates are based on preliminary correlation analysis between GM volume and various vascular and demographical factors)	HF (and CHD in lesser extent) was associated with lower volume in cingulate, middle temporal lobe, frontal and parieto-occipital cortex.

HF and AF can be related to CHD, but they can also occur and affect the brain independently of CHD (Roman, 2004, Stefansdottir et al., 2013). Previous studies of HF and brain morphology have had smaller sample sizes as compared to the CHD studies, but more innovative MRI methods have been used and the results seem to be more consistent. Three studies utilized an automatic whole brain segmentation method to evaluate possible relations between different brain regions and HF (Almeida et al., 2012, Woo et al., 2003, Woo et al., 2009). All three studies showed lower regional brain volumes throughout the whole cerebrum in people with HF compared to controls. Temporal lobe, cingulate and insular cortex were particularly affected. Visually rated MTA was more pronounced in patients with HF (Beer et al., 2009, Vogels et al., 2007), and a general GM volume loss was also seen (Bhattacharya et al., 2012, Schmidt et al., 1991). Only one study detected an association between HF and WML (Vogels et al., 2007). In this study, the relationships of HF with MTA and WML were clearer as compared to CHD. Similar results were found in another study (Almeida et al., 2012), suggesting that the effects of HF on brain changes were at least partly independent of CHD. A small DTI study investigating middle-aged people showed decreased axonal integrity in autonomic, cognitive and emotional regulatory areas in HF patients as compared to controls (Kumar et al., 2011).

Six studies have so far focused on AF and structural brain changes. One study had a five year follow-up time (de Leeuw et al., 2000), another gathered information about disease duration (Stefansdottir et al., 2013), while the rest were cross-sectional (Knecht et al., 2008, Kobayashi et al., 2012, Manolio et al., 1994, Seshadri et al., 2004). A large Icelandic cohort study detected a significant association of AF with lower total and GM volumes and more WML (Stefansdottir et al., 2013). The association with total brain and GM volumes was stronger for persistent AF and for longer disease duration, which may explain the earlier negative results (Knecht et al., 2008, Manolio et al., 1994, Seshadri et al., 2004). The manually traced hippocampal volume in a sample of subjects without dementia was lower in individuals with AF compared to controls (Knecht et al., 2008). AF was associated with WML in two other populations (de Leeuw et al., 2000, Kobayashi et al., 2012).

2.3.3 Heart diseases and dementia - possible mechanisms of association

The effects of heart diseases on the brain may be partly related to vascular risk factors such as hypertension or hypercholesterolemia. However, findings from several studies focusing on structural brain changes and heart diseases remained significant even after adjustments for vascular risk factors, and thus other mechanisms may also exist. In patients with HF, left ventricular dysfunction together with impaired brain arterial autoregulation may lead to cerebral hypoperfusion, especially in watershed areas such as periventricular WM, hippocampus and insula (Roman, 2004). Hypercoagulopathy occurs in AF due to impaired blood flow in the atriums of the heart, predisposing patients to embolic strokes. Apart from major strokes affecting the large arteries, microembolisms may also occlude small arterioles causing microinfarcts and subsequent atrophy

(Stefansdottir et al., 2013). Furthermore, both CHD and AF may cause left ventricular dysfunction leading to cerebral hypoperfusion. CHD may additionally reflect systemic atherosclerosis affecting small cerebral arteries/arterioles, with vessel occlusion and microinfarcts.

2.4. RISK ESTIMATION TOOLS FOR PREDICTING DEMENTIA

At present, two dementia risk scores based on demographic, lifestyle and vascular risk factors have been developed (Kivipelto et al., 2006, Mitnitski et al., 2006). The CAIDE Dementia Risk Score estimates the risk of dementia occuring 20 to 40 years later based on the midlife risk profile (Exalto et al., 2013, Kivipelto et al., 2006); it achieved moderate prediction accuracy both in the original and in a validation study (area under curve [AUC] 0.77 and 0.75, respectively). The CAIDE Dementia Risk Score consists of easily measurable factors (age, sex, education, SBP, BMI, total cholesterol, physical activity), which makes it easy to use in general practice settings. Another risk index included 23 different vascular risk factors (+sex) and was developed to predict the risk of dementia and death after 10 and 20 years (Mitnitski et al., 2006). The accuracy of distinction between individuals without dementia and those with dementia was moderate after 10 years (AUC 0.74), and decreased when the follow-up time was prolonged to 20 years (AUC 0.67).

A more complex dementia risk index was developed to predict shorter-term dementia risk in older individuals (Barnes et al., 2009). This risk index showed slightly better separation accuracy (AUC 0.81) than the CAIDE Dementia Risk Score, but it also contains more laborious variables such as cognitive and physical tests, neuroimaging parameters and internal carotid artery wall thickness. A simplified version of the risk index has also been published (Brief Dementia Risk Index [BDRI]), providing almost as good separation accuracy (AUC 0.77) between individuals with and without dementia as the original risk index (Barnes et al., 2010).

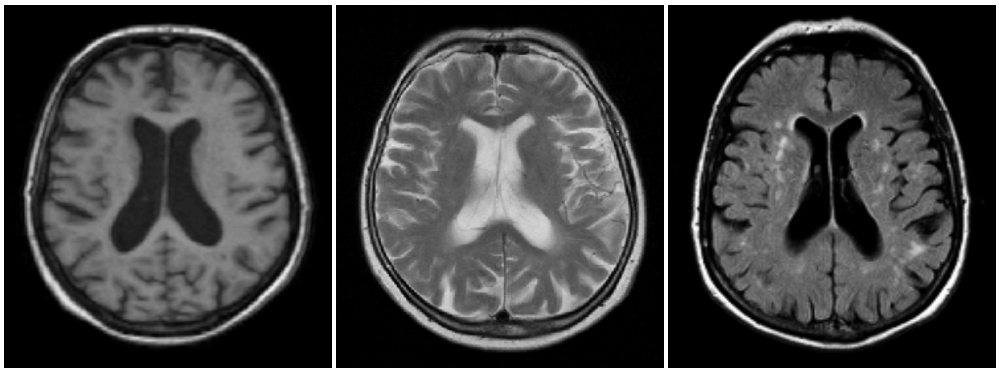
In another study, aggregation of factors related to atherosclerosis (high SBP, diabetes/prediabetes, stroke) or brain hypoperfusion (low DBP and pulse pressure [PP], HF) was shown to approximately double the dementia risk in elderly people after nine years of follow-up (Qiu et al., 2010). Interestingly, the Framingham general cardiovascular disease risk score (D'Agostino RB et al., 2008) and Framingham stroke risk score (D'Agostino et al., 1994) showed slightly stronger associations with the cognitive decline in multiple domains as compared to the CAIDE Dementia Risk Score in a large British longitudinal study (Kaffashian et al., 2013). Dementia diagnoses were not available in that study, which may partly explain the results. There were also notable differences between risk score variables. For example, both Framingham risk scores included diabetes (which is not included in CAIDE Dementia Risk Score), and diabetes showed the strongest independent association with cognition of all the variables evaluated in that study. However, in a large Northern American cohort, dementia predictability was not improved when diabetes or several other risk factors were added to the CAIDE Dementia Risk Score

(Exalto et al., 2013). The risk scores based on demographic, physical and vascular risk factors seem to predict dementia well, but it is still unknown whether they relate to vascular more than to neurodegenerative pathologies. The Framingham cardiovascular risk profile was inversely associated with GM volume and thickness in a cross-sectional study (Cardenas et al., 2012), but these associations need to be investigated in longitudinal studies.

2.5. STRUCTURAL MRI AND THE AGING BRAIN

2.5.1 Basic MRI sequences in dementia-related disorders

T1, T2, and Fluid Attenuated Inversion Recovery (FLAIR) are the basic sequences most often used for dementia-related disorders. In addition, diffusion weighted imaging (DWI) has been used for younger patients or in rapidly progressive disease forms, and T2* is especially good for detecting microbleeds. T1-weighted MRI may be considered as an "anatomy scan" due to its good ability to separate fluid from fat, providing an appreciable contrast between GM and WM (Figure 2). T1-weighted MRI can also be acquired rapidly due to its short repetition time (TR). T2-weighted MRI is called the "pathology scan" because of its ability to identify edema (e.g. around tumors) and small infarcts. T2-weighted images take longer to acquire due to the prolonged TR. FLAIR-weighting is similar to T2, but in FLAIR, the signal from fluids is attenuated (fluids are black). This makes easier the separation between CSF and WML.



T1-weighted T2-weighted FLAIR

Figure 2. The basic MR sequences used in memory disorder imaging

2.5.2 MRI and brain structures – visual methods

Most visual rating scales were initially developed for research use, but due to their rapidity and sufficient accuracy, some of them have become established in clinical settings. The most widely used visual rating scale for MTA evaluates the width of the choroid fissure and temporal horn and volume loss of hippocampus (Figure 3) (Scheltens et al., 1992). The Scheltens scale has proved to be good at separating healthy controls from patients with AD, with specificity and sensitivity values of 76-

90% and 70-90%, respectively (Scheltens et al., 1997, Wahlund et al., 2000). The Scheltens scale showed slightly lower accuracy as compared to automatic and manual segmentation of hippocampus when distinguishing healthy controls from patients with AD. However, the differences were small, especially between visual rating and automatic segmentation (81% and 83%, respectively) (Westman et al., 2011).

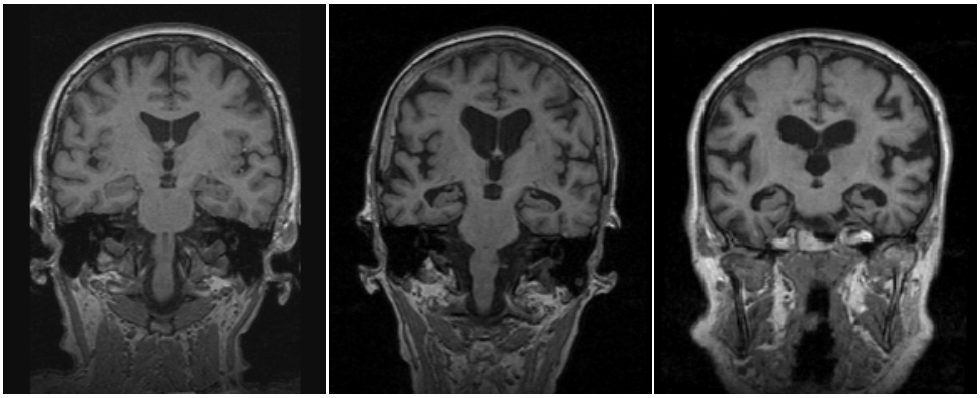


Figure 3. Visual rating of MTA on CAIDE participants. No medial temporal lobe atrophy was seen in the first coronal T1-image (MTA=0 bilaterally; control subject). In the second image, MTA was scored as 2 bilaterally (control). In the last image, MTA was scored as 3 on the left side and 2 on the right side (AD).

MTA is of special interest in the evaluation of memory clinic patients, but radiological assessment of vascular changes is also important. Several visual rating scales for evaluating WML have been developed (Mantyla et al., 1997, Wahlund et al., 2001). There are differences between rating scales and these need to be considered when comparing the results from different studies (Mantyla et al., 1997). The simplest scales do not differentiate between periventricular WML, subcortical WML or regional positioning (Breteler et al., 1994, Herholz et al., 1990, Schmidt et al., 1992, Wahlund et al., 1990). More complex scales rate WM changes according to their size, anatomical position, type and formation (Scheltens et al., 1993). The highly reproducible and easily applicable Fazekas scale (Fazekas et al., 1987) is widely used in clinical settings and it shows a good correspondence with other more detailed scales (Scheltens et al., 1998). Similarly to the Fazekas scale, the Age-Related WM Changes (ARWMC) scale (Wahlund et al., 2001) uses a four-point rating system, but WML are divided based on their regional position. The ARWMC scale can be used with both MRI and CT (Figure 4). The characteristics of some of the WML rating scales are shown in Table 3.

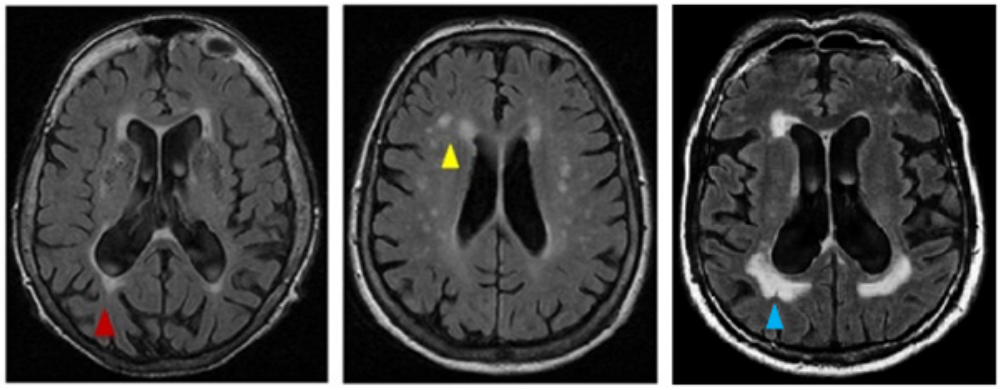


Figure 4. Example of the ARWMC rating scale on FLAIR MRI. The red arrow points to a rating score of 1 for the right parieto-occipital area. The yellow arrow indicates a rating score of 2 for the right frontal area. The blue arrow indicates a rating score of 3 for the right parieto-occipital area.

Table 3. Characteristics of selected WML rating scales

Scale	PWML/DWML	Lesion size/form	Regional position	Points
Fazekas (1987)	Distinct	Verbal	No	PWML: 0-3 DWML: 0-3
Schmidt (1992)	Combined	Verbal	No	WML: 0-3
Scheltens (1993)	Distinct	Numerical	Yes	PWML: 0-6 DWML: 0-24 BGWML: 0-30 ITWML: 0-24
ARWMC (2001)	Combined	Verbal	Yes	WML: 0-24* BGWML: 0-6*

PWML=periventricular WML; DWML=deep WML; ITWML=infratentorial WML; BGWML=basal ganglia WML
*Left and right hemispheres are rated separately.

2.5.3 MRI and brain structures – manual and automatic methods

Visual rating scales provide qualitative and, at best, semi-quantitative data, but GM structures and WML can also be delineated by hand in order to obtain quantitative volumes. For example, at least 71 different manual delineating protocols for hippocampus have been published (Konrad et al., 2009). In principle, any brain structure or pathology with clear boundaries can be manually segmented (Goldstein et al., 2005, Looi et al., 2008, Raz et al., 1997). Manual delineation of hippocampus is considered to be the golden standard when studying hippocampal volume, and findings from a recent study of the accuracy in predicting AD based on hippocampal manual, automated and visual analysis confirm this view (Westman et al., 2011). Although it has a better segmentation accuracy, manual segmentation is a laborious

and time consuming process. All visual rating and manual delineation methods are also operator-sensitive, leaving space for human error.

Automatic whole-brain analysis methods have become more common in past decade. These methods enable the inspection of multiple brain structures without a prior hypothesis. Several automatic cerebral cortex thickness measuring pipelines are available (Fischl and Dale, 2000, Jones et al., 2000, Lerch and Evans, 2005, MacDonald et al., 2000), and one of the most widely used is *FreeSurfer,* a freeware software published by Fischl and Dale in 2000. FreeSurfer is actually a set of software tools, because in addition to cortical thickness measurements, it can also provide cortical and subcortical volumes. The procedure published by Lerch and Evans (*Montreal method*) is similar to FreeSurfer, with some methodological differences (http://www.bic.mni.mcgill.ca/). For example, the pipelines use different distance metrics which may produce variations in results, but the differences are probably not so pronounced (Lerch and Evans, 2005). An overview of the steps involved in the Montreal method is presented in Figure 5.

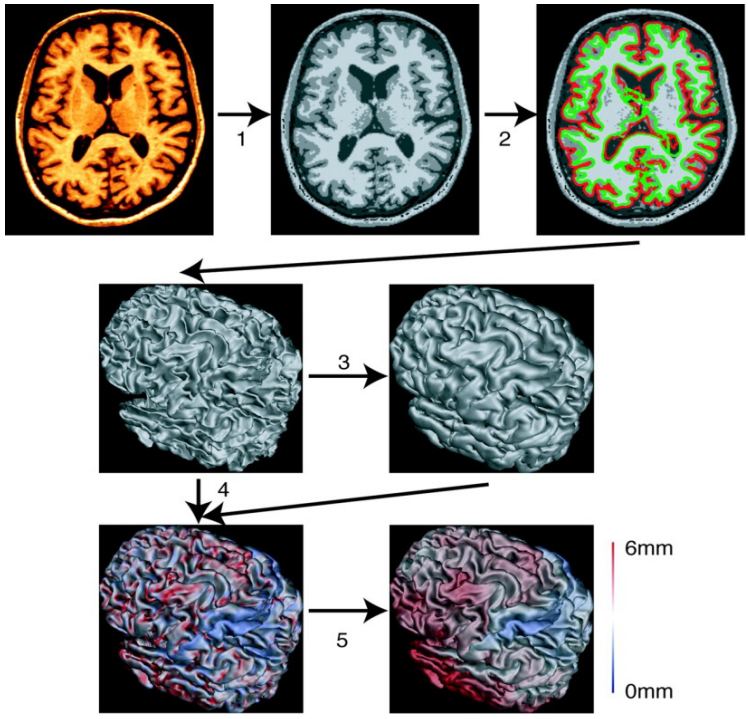


Figure 5. Overview of the Montreal method steps for cortical thickness analysis. First, images are non-uniformity corrected and registered into stereotaxic space. They are then classified (1) and fitted with a WM surface (2). The GM surface is found by expanding out from the WM surface (3). Cortical thickness is measured at every vertex (4), and blurred using a 20 mm surface-based kernel (5). Reprinted from Lerch et al. (2005) with permission from Oxford University Press.

Similarly to the situation with GM structures, WML manual delineation is laborious and time consuming. For this reason, there is a great need for automatic analysing procedures. Most automatic WML analysing methods use training data sets and machine learning algorithms for classifying voxels as WML or normal intracranial tissue/fluid (Anbeek et al., 2004, Damangir et al., 2012, Johnston et al., 1996, Khayati et al., 2008, Lao et al., 2008). Methods relying purely on voxel intensities also exist, but they tend to produce a high number of false positives (Kloppel et al., 2011). With respect to the machine learning algorithms, methods using support vector machine (SVM) seem to perform best and the results are even more accurate when information is included about neighboring voxels and anatomy (Kloppel et al., 2011).

Automatic brain segmentation methods have advanced significantly during the past 10-15 years, and the progress will continue in parallel with evolving MR cameras and computer power. Fully-automatic methods are fast, operator-independent (except for the planning, coding and quality check phases), less labor compared to manual methods, and are becoming increasingly robust. In general, visual rating methods are still mainly used in the clinic, but this can be predicted to change in the future. For example, automatic hippocampal segmentation can be done in about two minutes using a basic laptop computer (Lotjonen et al., 2011). Automatic segmentation of small structures such as the entorhinal cortex is more difficult, mainly because of the insufficient resolution of basic MR cameras. In addition, tissue intensity variation in GM nuclei (Fischl, 2012), relatively hazy borders of WML (Kloppel et al., 2011) and advanced atrophy (Chupin et al., 2009) are still challenging for automatic segmentation methods. For these reasons, the quality check of segmentation results by a human operator is still an important component of structural brain imaging research.

3 Aims of the Study

The general aim of the thesis was to investigate long-term associations between vascular risk factors and conditions from midlife to late-life and dementia-related structural brain changes on MRI in late-life. The specific aims were:

1) To study the associations of midlife blood pressure, BMI and total cholesterol with WML two decades later; to investigate changes in blood pressure, BMI and cholesterol during 20 years after midlife in relation to WML, as well as the effects of APOE genotype (Study I).

2) To study the relationships between midlife blood pressure, BMI, total cholesterol, their changes over time and regional cortical thickness measured up to 30 years later (Study II).

3) To investigate the long-term effects of CHD on cortical thickness, GM volume, and WML volume, taking into account the possible modifying effect of blood pressure (Study III).

4) To evaluate the associations between the CAIDE Dementia Risk Score in midlife and cortical thickness, GM volume, MTA, and WML up to 30 years later (Study IV).

4 Subjects and Methods

4.1 CAIDE STUDY AND MRI POPULATIONS

All four studies in the thesis were based on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study carried out in Eastern Finland. CAIDE is a longitudinal, population-based study focusing on associations of cardiovascular and lifestyle-related risk factors with dementia and cognitive functioning. CAIDE participants were first evaluated at midlife in 1972, 1977, 1982 or 1987 within the North Karelia Project and the Finnish part of Monitoring Trends and Determinants in Cardiovascular Disease (FINMONICA) study (Puska et al., 1979, Puska et al., 1983, Vartiainen et al., 1994). These studies were conducted to evaluate the risk factors, morbidity and mortality related to cardiovascular diseases. In 1972 and 1977, a random sample of 6.6% of the population born in 1913-1947 and living in Kuopio and North Karelia provinces was drawn. In 1982 and 1987, the stratified sample of persons aged 25-64 years and living in Kuopio or North Karelia provinces (250 subjects of each sex and 10-year age group from both provinces) was chosen based on the international WHO MONICA project protocol (WHO MONICA Project Principal Investigators, 1988).

The CAIDE study and formation of the MRI populations are presented in Figure 6. A random sample of 2000 participants in the North Karelia Project or FINMONICA study, aged 65-79 years at the end of 1997, and living in or close to the towns of Kuopio and Joensuu were invited to participate at the first re-examination in 1998 (Kivipelto et al., 2001a). Altogether 1449 (72.5%) individuals participated (Kivipelto et al., 2001b) and 61 subjects were diagnosed with dementia (AD, n=48) and 82 subjects with MCI. A second re-examination was conducted in 2005-2008. All 1426 persons of the original 2000 who were still alive and living in the geographical area of Kuopio or Joensuu were invited, and 909 (63.7%) participated. 68 subjects were diagnosed with dementia (AD, n=57) and 171 with MCI. Cognitive status was assessed at both re-examinations with a three-step protocol: screening phase, clinical phase, and differential diagnostic phase (including brain MRI). The CAIDE MRI population at the first re-examination (n=112 participants) included all dementia cases from the Kuopio region (n=39), sex- and age- (± 3 years) matched subjects with MCI (n=31), and at least one similarly matched cognitively normal control (n=42) for each dementia case. The CAIDE MRI population at the second re-examination (n=113) included all subjects from the Kuopio cohort attending the differential diagnostic phase: 37 with dementia, 70 with MCI, and 6 defined as controls. Only 18 participants were included in both CAIDE MRI populations.

The CAIDE study was approved by the local ethics committee of Kuopio University Hospital and written informed consent was obtained from all participants.

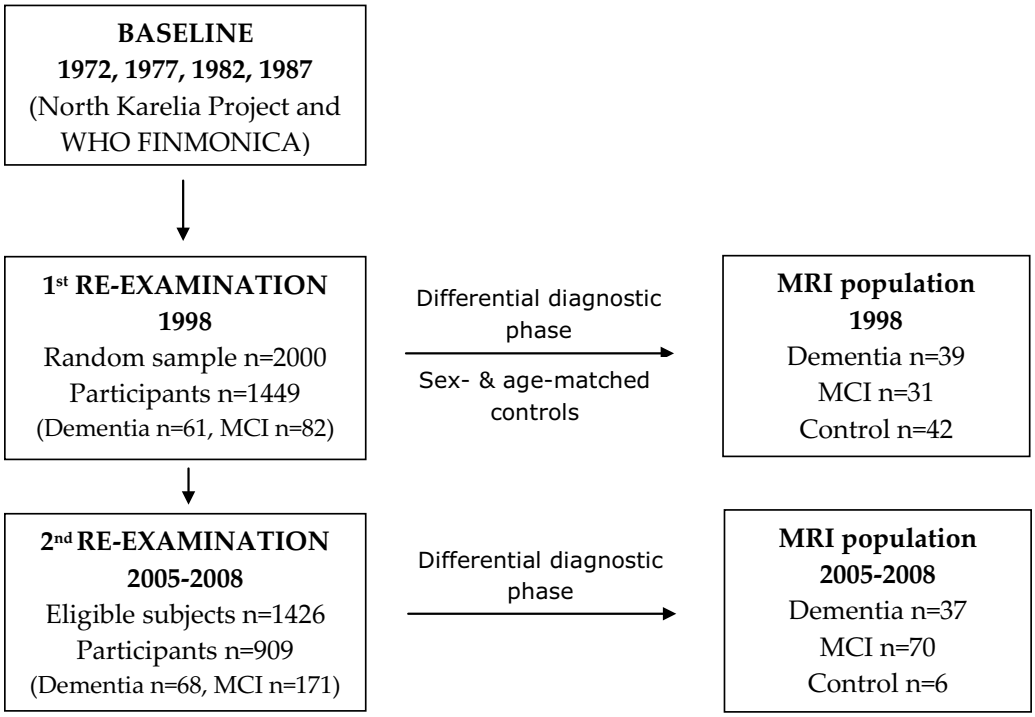


Figure 6. CAIDE study and formation of the MRI populations.

4.2 MRI METHODS

4.2.1 First CAIDE re-examination (1998)

Participants in the differential diagnostic phase of the first re-examination were scanned using a 1.5 T MR unit (Magnetom Vision Format; Siemens) at Kuopio University Hospital. MRI protocol included T1, T2, proton density (PD) and FLAIR sequences. All images were visually checked by an experienced neuroradiologist to confirm that they were free of artifacts and clinically significant brain conditions such as tumors, major post-stroke lesions or normal pressure hydrocephalus.

Axial FLAIR images (repetition time [TR]=9000 ms, echo time [TE]=119 ms, flip angle=180°, field of view [FOV]=24 cm, Matrix=256x256, slice thickness=5 mm, in plane voxel dimension=0.94x0.94) were used to assess WML with a semi-quantitative visual rating scale (Wahlund et al., 2001) by a single trained rater blinded to the possible diagnoses and other clinical data. The lesions were rated separately for five brain regions (frontal, parieto-occipital, temporal, infratentorial and basal ganglia) in both hemispheres. Except for the basal ganglia, the rating was done using a 4-

stepped scale: 0=no changes, 1=focal lesions, 2=incipient confluence of lesions and 3=diffuse involvement of the entire region, with or without involvement of U fibres. Changes in basal ganglia were similarly rated: 0=no changes, 1=focal lesion (≤5 mm), 2=more than one focal lesion and 3=confluent lesions. The total WML burden was calculated by summing the ratings from all of the separate brain regions from both hemispheres. Re-rating of a sub-sample of the images resulted in intra-rater correlation coefficient of r=0.98. In addition, the reliability of the WML rating was confirmed by an external rater also blinded to the diagnoses and any of the clinical data at the time of rating. Comparison of these two ratings led to an inter-rater correlation coefficient value of r=0.90.

T1-weighted images were assesed using three dimensional magnetization prepared rapid acquisition gradient echo (3D-MPRAGE) sequence (TR=9.7ms, TE=4ms, flip angle=12°, FOV=25cm, matrix 256x256, slice thickness=2mm, in plane voxel dimension=0.98x0.98mm). A single trained rater assessed MTA from T1-weighted images according to a visual rating scale commonly used in clinical practice (Scheltens et al., 1992). MRIs were oriented perpendicular to the anterior commisure - posterior commisure line and MTA was rated from a single coronal slice at the level where hippocampus, cerebral peduncles and pons were all visible. MTA was graded from zero (no atrophy) to four (end-stage atrophy) bilaterally.

GM volumes were measured using FAST FSL (FMRIB's Automated Segmentation Tool) (Zhang et al., 2001). FAST segments a 3D MRI of the brain into different tissue types (GM, WM, CSF), whilst also correcting for spatial intensity variations (also known as bias field or radio frequency inhomogeneities). The underlying method is based on a hidden Markov random field model and an associated Expectation-Maximization algorithm. The whole process is fully automated and can also produce a bias field-corrected input image and probabilistic and/or partial volume tissue segmentation.

4.2.2 Second CAIDE re-examination (2005-2008)

Participants in the differential diagnostic phase of the second re-examination were scanned using two different 1.5 T MR units (Magnetom Vision or Avanto; Siemens) at Kuopio University Hospital. The MRI protocol included T1, T2, PD and FLAIR sequences, and additionally DWI and T2* sequences. All images were visually checked by an experienced neuroradiologist to confirm that they were free of artifacts and clinically significant brain conditions such as tumors, major post-stroke lesions or normal pressure hydrocephalus.

3D-MPRAGE T1-weighted MRIs were used for cortical thickness and GM volume measurements. The imaging parameters were: Magnetom Vision (TR=9.7 ms, TE=4.0 ms, TI=300 ms, FA=12°, slice thickness=1.5-2.0 mm, matrix 256x256, number of slices=128 or 148) and Avanto (TR=1900 ms, TE=3.93 ms, TI=1100 ms, FA=15°, slice thickness=1.0-1.5 mm, matrix 384/448x512, number of slices=160). Data were analysed using algorithms developed at McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Canada

(http://www.bic.mni.mcgill.ca/). Initially, individual native MRIs were registered into standardized stereotaxic space using the ICBM 152 template and corrected for intensity non-uniformity using the N3 algorithm. The N3 algorithm is a fully automated technique which maximizes the entropy of the intensity histogram and can be applied to any pulse sequences, field strength or MR scanner. Subsequently, the images were segmented into GM, WM and CSF using an artificial neural network classifier termed INSECT (Intensity-Normalized Stereotaxic Environment for Classification of Tissues) (Zijdenbos, 1998). 3D brain mask was calculated to remove extra-cerebral voxels and partial volume effect (PVE) was estimated. Surfaces between GM and WM (WM surface=WMS) as well as GM and CSF (GM surface=GMS) were defined using Constrained Laplacian-based Automated Segmentation with Proximities (CLASP) algorithm (Kim et al., 2005). Each polygon mesh surface consisted of 81 920 polygons and 40 962 nodes per hemisphere. Cortical thickness was defined as the distance between each vertex on WMS and its counterpart/linked vertex on GMS. Thickness calculations were performed in native space and thereafter transformed back to standardized space to enable group analysis. In the final step, cortical thickness maps were smoothed using 20 mm full width at half maximum diffusion kernel to increase the signal-to-noise ratio and to have more normally distributed data. Finally, the outcome of the pipeline was inspected visually to ascertain the quality of the surface estimation.

FLAIR parameters were: TR=9000 ms, TE=119 ms, TI=2200 ms, slice thickness=5 mm, flip angle=180°, matrix=512x168. WML volumes were calculated from T1- and FLAIR-images using an automatic pipeline developed at Karolinska Institute, Stockholm, Sweden (www.github.com/Damangir/Cascade) (Damangir et al., 2012). Pre-processing steps included affine registration of T1- to FLAIR-images; followed by brain extraction (Smith, 2002). Manual quality control was performed to inspect the brain extraction quality. Then brain tissues segmentation (Zhang et al., 2001) and histogram matching was carried out for both sequences. In the main classification, each voxel was classified as WML or normal based on the intensities of neighboring voxels on T1- and FLAIR-images. Voxels classified as normal were pruned away from cascade while the rest proceeded to the next step. Finally after multiple classification steps, only voxels classified as WML were left. Next morphological and spatial filtering was done to remove WML detections that were too small or in dissimilar spatial locations (e.g. in CSF). Finally all detections passed through boundary refining and the final output consisted of volumes and masks of the WML. By using this novel cascade method, high sensitivity (90%) and specificity (99.5%) was achieved when compared to manual delineation of WML (Damangir et al., 2012).

MTA rating in the second re-examination was performed identically to the first re-examination.

4.3 COGNITIVE ASSESSMENTS

Cognitive status was assessed in both CAIDE re-examinations with a three-step protocol: screening phase, clinical phase, and differential diagnostic phase.

In the screening phase, each participant and an informant were initially interviewed. A specially trained study nurse then carried out preliminary cognitive testing including Mini-Mental State Examination (MMSE) (Folstein et al., 1975), immediate word recall test (Heun et al., 1998, Nyberg et al., 1997), category fluency test (Borkowski et al., 1967), Purdue Peg Board test (Tiffin, 1968), letter-digit substitution test (Wechsler, 1944), Stroop test (Stroop, 1935), prospective memory task (Einstein et al., 1997) and subjective memory rating (Bennett-Levy and Powell, 1980). In the first re-examination in 1998, participants scoring 24 or less in the MMSE were referred to clinical phase. In the second re-examination in 2005-2008, screening criteria were modified to improve sensitivity to detect MCI and mild forms of dementia: 1) MMSE 24 points or less, 2) decline in MMSE of three or more points since the first re-examination, 3) delayed recall word list test <70% in the Finnish version of CERAD test battery, or 4) report of cognitive decline by the informant.

The clinical phase included a detailed cardiovascular and neurological examination performed by the study physician, and comprehensive cognitive testing by the study neuropsychologist. Participants judged to have possible dementia were referred to the differential diagnostic phase which included blood tests, chest radiograph, electrocardiogram, brain MRI or CT, and CSF analysis if needed. All available information was evaluated by a review board consisting of a senior neurologist, senior neuropsychologist, study physician and study neuropsychologist, and the final diagnosis was established.

Dementia was diagnosed according to the DSM-IV criteria (American Psychiatric Association, 1994), and AD according to the NINCDS-ADRDA criteria (McKhann et al., 1984). All individuals diagnosed with AD showed general and/or medial temporal lobe atrophy and no significant vascular pathology was observed on MRI/CT. Isolated, minor lacunar infarcts or moderate WML were not considered as exclusion criteria. Patients with AD scored four points or less on the Hachinski Ischemia Scale (Hachinski et al., 1975). The NINDS-AIREN criteria were used to diagnose VaD (Roman et al., 1993). Consensus criteria were used for diagnosing frontotemporal dementia (Neary et al., 1998), dementia with Lewy bodies (McKeith et al., 1996) and alcohol-related dementia (Oslin et al., 1998). A modified version of the Mayo Clinic Alzheimer's Disease Research Center criteria was used to identify MCI (Petersen et al., 1995): 1) memory complaint by patient, family, or physician, 2) normal activities of daily living, 3) normal global cognitive function, 4) objective impairment of memory or other areas of cognitive functioning as evidenced by scores >1.5 standard deviations (SD) below the age-appropriate mean, 5) Clinical Dementia Rating (CDR) score of 0.5, and 6) absence of dementia.

4.4 ASSESSMENT OF VASCULAR FACTORS AND CONDITIONS

4.4.1 Baseline (midlife) examination

Survey methods used during the baseline visit were standardized according to international recommendations. They followed the WHO MONICA protocol in 1982 and 1987, and were comparable with the methods used in 1972 and 1977 (Kuulasmaa et al., 2000). The baseline surveys included a self-administered questionnaire on health behaviors, health status and medical history. The questionnaire was mailed to the participants prior to their visit and a trained nurse checked that the questionnaire was fully completed. BP was measured from subject's right arm after they had been seated for five minutes. A non-fasting venous blood specimen was taken to determine the serum cholesterol level. Serum cholesterol concentrations were measured in the years 1972 and 1977 from frozen serum using Lieberman-Burchard method. Instead, in 1982 and 1987 serum cholesterol concentrations were measured from fresh serum using the enzymatic cholesterol oxidase/p-aminophenazone (CHOD-PAP) method. There was a systematic difference (2.4%) between cholesterol measurement methods, and because of that, the results were corrected accordingly (Sundvall et al., 2007). All cholesterol levels were determined in the same central laboratory and the laboratory data were standardized with the national and international reference laboratories. Participants' height (m) and weight (kg) were measured and BMI was calculated (kg/m^2).

4.4.2 First and second CAIDE re-examinations

Survey methods used during the first and second re-examinations were identical to those used during the midlife visit in all major aspects. In addition to the midlife self-administered questionnaire, drug use and psychosocial factors were enquired. The APOE-genotypes were assessed from blood leucocytes using polymerase chain reaction and HhaI digestion (Tsukamoto et al., 1993).

4.4.3 Coronary heart disease diagnosis in the Finnish Hospital Discharge Register

The Finnish Hospital Discharge Register is maintained by the National Institute for Health and Welfare. This includes information on in-patient stays in public hospitals (i.e. main reason of hospitalization; other diseases/conditions are recorded to a lesser extent) starting from 1969. Information from out-patient clinics, health centers or private hospitals is not included. Diagnoses are based on ICD-codes. ICD-8 was used in Finland during 1969-1986, ICD-9 during 1987-1995, and ICD-10 from 1996 onwards. The identification of the persons in the register is based on the unique identification code, which is given to every resident in Finland. CHD diagnoses were obtained using the following ICD codes: 410-414 (ICD-8); 410-414 (ICD-9); I20-I25 (ICD-10).

4.4.4 CAIDE Dementia Risk Score

The midlife CAIDE Dementia Risk Score for each participant was calculated according to previously specified cut-offs and number of points (Table 4) (Kivipelto

et al., 2006). Two versions of the CAIDE risk score were calculated based on the initial publication: basic model including age, gender, education, SBP, total cholesterol, BMI and leisure-time physical activity (range 0-15 points); and APOE model additionally including APOE4 carrier status (range 0-18 points). Assessment of the factors used in CAIDE Dementia Risk Score is described in 4.4.1 and 4.4.2. Physical activity was assessed with the question: 'How often do you participate in leisure-time physical activity that lasts at least 20-30 minutes and causes breathlessness and sweating?' Response options were: 1) daily; 2) 2-3 times a week; 3) once a week; 4) 2-3 times a month; 5) a few times a year; and 6) not at all. Participants who engaged in physical activity at least twice a week (options 1 or 2) were regarded as active, and the others as inactive.

Table 4. CAIDE Dementia Risk Score factors and number of points

	Model 1 (without APOE)	**Model 2 (with APOE)**
Age		
<47 years	0	0
47-53 years	3	3
>53 years	4	5
Education		
≥10 years	0	0
7-9 years	2	3
0-6 years	3	4
Sex		
Women	0	0
Men	1	1
Systolic blood pressure		
≤140 mmHg	0	0
>140 mmHg	2	2
Body-mass index		
≤30 kg/m^2	0	0
>30 kg/m^2	2	2
Total cholesterol		
≤6.5 mmol/l	0	0
>6.5 mmol/l	2	1
Physical activity		
Active	0	0
Inactive	1	1
APOE ε4 status		
Non-carrier	-	0
Carrier	-	2
Total number of points	Max. 15 points	Max. 18 points

4.5 STATISTICAL ANALYSES

4.5.1 Study I

Study I included the CAIDE MRI population from the first re-examination (n=112). The focus was on midlife BP, BMI and total cholesterol, their changes from midlife to the first re-examination, and APOE genotype in relation to WML at the first re-examination. The distribution of the subjects with dementia (n=39), and age- and sex-matched MCI (n=31) or controls (n=42) did not match the distribution in the original CAIDE population. In order to ensure representativeness, the data was weighted for the inverse of the probability of each person from the original CAIDE population to be included in the 1998 MRI population.

Participants were categorized according to the total WML score as follows: no/mild WML (≤4 points), moderate WML (5-7 points) and severe WML (≥ 8 points). χ^2-test and ordinal regression analyses were used to calculate p-values for the descriptive statistical differences between WML groups. Ordinal regression analyses were also used for calculating odds ratios (OR) and 95% confidence intervals (CI) for the associations between BP, BMI, total serum cholesterol, APOE and WML. As WML are common findings in the elderly, ORs cannot be used meaningfully as an estimate for risk. Therefore, the risk ratios (RR) were calculated from the ORs using a previously published formula which better represents the true relative risk (Zhang and Yu, 1998). The original formula was modified to fit the model with trichotomous outcome as a dependent variable.

The participants with SBP ≥160 mmHg and/or DBP ≥90 mmHg were considered hypertensive. Subjects with BMI 25-30 were considered as overweight, and those with BMI 30 kg/m^2 or more were classified as obese. The cut-off for high total cholesterol was considered to be 6.5 mmol/l, because of the generally high serum total cholesterol values in the study population. APOE4 carriers were categorised as heterozygous (one APOE ε4 allele) and homozygous (both APOE ε4 alleles). Analyses were adjusted for socio-demographic factors including sex, age, education and follow-up time, and also self-reported antihypertensive treatment (hypertension analyses) and lipid-lowering treatment (cholesterol analyses) (model 1). Additional adjustments were done for the diagnosis of dementia/MCI, APOE carrier status, self-reported smoking and alcohol use and vascular factors (SBP, DBP and cholesterol in BMI analyses; cholesterol and BMI in hypertension analyses; and SBP, DBP and BMI in cholesterol analyses) (model 2). The level of significance was $p<0.05$ in all analyses. All statistical analyses were done using SPSS 17.0.

4.5.2 Study II

Study II included 63 individuals without dementia from the CAIDE MRI population in the second re-examination. These participants had MRIs of adequate quality to permit cortical thickness measurements. Suitability of MRIs for cortical thickness analyses was evaluated visually based on successfulness of registration and segmentation and also for the presence of artifacts. MRIs were graded from 0 to 3

(0=very suitable, 3=not suitable) and all MRIs graded as 3 (n=7) were excluded. Data weighting could not be used in the CAIDE 2005-2008 MRI population to ensure representativeness for the original CAIDE population. Subjects with dementia (n=37) were excluded from the study, and analyses were focused on elderly subjects at risk of dementia.

Study II focused on midlife BP, BMI, total cholesterol, their changes from midlife to the second re-examination, and APOE genotype in relation to cortical thickness in the second re-examination. Statistical analyses were conducted in two steps. First, in-house scripts under Matlab R2008a (Mathworks Inc., Natick, Mass., USA) were used to identify brain regions significantly related to BP, BMI or cholesterol. The regions were identified based on group level analyses (significant differences in cortical thickness between subjects with midlife hypertension/controls; midlife overweight/controls; and hypercholesterolemia/controls) using a whole brain cortical thickness analysis method. Midlife hypertension was defined as SBP ≥160 mmHg and/or DBP ≥95 mmHg, overweight as BMI ≥25, and hypercholesterolemia as total cholesterol ≥7 mmol/L. The analyses were adjusted for age, sex, follow-up time, scanner type, antihypertensive treatment (in BP analyses), and lipid-lowering treatment (in cholesterol analyses). Information on BP- and cholesterol-lowering medication was obtained from the Drug Reimbursement Register in Finland. Parametric t-tests were performed for each vertex, and the results were corrected for multiple comparisons using the false discovery rate (FDR) technique (Genovese et al., 2002) ($p<0.05$).

In the second step of the analyses, mean cortical thickness was calculated for each selected brain region (the minimum size for a region to be selected was 50 nodes), and the absolute mean thickness value for each subject was exported to SPSS 19.0 (SPSS Inc., Chicago, IL, USA) for more detailed analyses. Since only hypertension was significantly associated with cortical thickness in the first step, the second step of statistical analyses focused on BP and related brain regions. Linear regression analyses were performed to investigate the links between midlife SBP, DBP and PP values and late-life cortical thickness (distribution of cortical thickness values was normalized with logarithmic transformations). General linear models for repeated measures were used for studying the relations between changes in SBP, DBP and PP from midlife to late-life and the cortical thickness in late-life. For each chosen brain area, cortical thickness values were categorized into two groups (lower versus higher) using the mean value as the cutoff. Analyses were adjusted for age, sex, follow-up time, scanner type, antihypertensive treatment and cardio/cerebrovascular conditions (self-reported myocardial infarction, heart failure, diabetes, or stroke/transient ischemic attack). Subjects' characteristics were also analysed with SPSS software using χ^2 for categorical variables and Student's t-test for continuous variables. The level of significance was set to $p<0.05$ in all analyses.

4.5.3 Study III

Study III included 69 individuals without dementia from the CAIDE MRI population at the second re-examination: the 63 participants in Study II and 6 additional subjects who screened as positive but did not fulfill criteria for MCI or dementia. These participants had MRIs of adequate quality for cortical thickness measurements. Study III focused on associations between CHD from midlife to second re-examination and cortical thickness, GM and WML volume at the second re-examination. Possible modifying effects of BP were also investigated.

Statistical analyses were performed in two steps. Regional cortical thicknesses were identified based on group level analyses (significant differences in cortical thickness between subjects with or without CHD). The mean absolute cortical thickness of these regions was calculated (the minimum size for a region to be selected for more detailed analyses was 100 nodes) and exported to SPSS 19.0. In the second step, relations between CHD, BP, cortical thickness and GM and WML volumes were analysed with SPSS using linear regression. Subjects' characteristics were analysed with SPSS software using χ^2 for categorical variables and Student's t-test for continuous variables.

Several definitions were used for CHD: all CHD diagnosed until the first CAIDE re-examination; all CHD diagnosed until the second re-examination; and CHD with shorter/longer duration. Duration of CHD was calculated as number of years between the first date of diagnosis and date of second CAIDE re-examination. Midlife hypertension was defined as SBP ≥160 and/or DBP ≥95 mmHg. All analyses were adjusted for age, sex, follow-up time and scanner type. Additionally, GM volume analyses were adjusted for TIV. WML volumes were log-transformed to normalize distribution. The results from linear regression analyses are presented as standardized β-coefficients (p-values). The level of significance was set at $p<0.05$ in all analyses.

4.5.4 Study IV

Study IV included both CAIDE MRI populations from the first (n=112) and second (n=69) re-examinations. As in Study I, data from the first re-examination were weighted for the inverse of the probability of each person from the original CAIDE population to be included in the 1998 MRI population, in order to ensure representativeness. Study IV focused on associations between CAIDE Dementia Risk Score at midlife and cortical thickness, GM volume, WML volume, and visual ratings of WML and MTA on MRI at the first or second re-examination.

Statistical analyses were done using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). The level of statistical significance was $p<0.05$ in all analyses. The CAIDE Dementia Risk Score at midlife was categorized as <10 points or≥10 points (version without APOE), and <11 points or ≥11 points (version with APOE).

MRI outcomes in the first re-examination: The total WML visual rating score was categorized as no/mild WML (≦7 points) and moderate/severe WML (≥8 points). The sum of left and right visual MTA ratings was calculated, and MTA was categorized

as no atrophy (0-1 points) and mild to severe atrophy (2-5 points). Logistic regression analyses were used to calculate ORs and 95% CIs for the associations between CAIDE Dementia Risk Score and WML and MTA ratings. Analyses were adjusted for follow-up time. Since WML and MTA are common at older ages, ORs cannot be used meaningfully as an estimate for risk. Therefore, RRs were calculated from ORs using a previously published formula which better represents the true relative risks (Zhang and Yu, 1998). Linear regression analyses were used for calculating standardized beta-coefficients (β) and p-values for the associations between CAIDE Dementia Risk Score and GM volume. The analyses were adjusted for follow-up time and TIV.

MRI outcomes in the second re-examination: The sum of left and right visual MTA ratings was calculated, and MTA was categorized as no atrophy (0-2 points) and mild to severe atrophy (3-5 points). The cut-off was increased to 3 points because MTA scores were generally higher compared to the first re-examination. Logistic regression was used to analyse the relation between CAIDE Dementia Risk Score and MTA (model adjusted for follow-up time and scanner type), and RR (95% CI) was calculated from OR (95% CI). WML volumes were log-transformed to normalize distribution, and linear regression was used to analyse associations between CAIDE Dementia Risk Score and WML volume (model adjusted for follow-up time and scanner type), or GM volume (model adjusted for follow-up time, scanner type and TIV). Relations between CAIDE Dementia Risk Score and regional cortical thickness were evaluated using in-house scripts under Matlab R2008a (Mathworks Inc., Natick, Mass., USA) as previously described. In the group level analyses, parametric t-tests were performed for each vertex, and results were corrected for multiple comparisons using the FDR technique (Genovese et al., 2002) ($p<0.05$).

5 Results

5.1 CHARACTERISTICS OF THE CAIDE MRI POPULATIONS

Sociodemographic and clinical characteristics of the two MRI populations in the first and second re-examination are shown in Table 5.

Table 5. Characteristics of MRI populations in the 1st and 2nd CAIDE re-examinations

Characteristics	**N**	**MRI in 1st re-examination (n=112)**		**N**	**MRI in 2nd re-examination (n=69)**
Age in midlife, years (SD)	112	50.63 (5.14)		69	49.88 (6.02)
Age in re-examination, years (SD)	112	72.85 (3.85)		69	77.89 (3.50)
Sex (men), n (%)	112	40 (35.4)		69	27 (39.1)
Education, years (SD)	110	7.29 (2.68)		67	7.79 (2.59)
Total follow-up time, years (SD)	112	22.03 (3.22)		69	28.01 (4.75)
Midlife SBP, mmHg (SD)	112	144.71 (20.67)		69	148.86 (24.79)
Midlife BMI, kg/m^2 (SD)	112	26.92 (3.63)		69	26.63 (4.20)
Midlife cholesterol, mmol/l (SD)	112	7.18 (1.22)		69	7.05 (1.17)
Midlife physical activity (active), n (%)	109	43 (39.4)		68	26 (38.2)
APOE status (carrier), n (%)	105	41 (39.1)		57	22 (38.6)
CAIDE Risk Score model 1, median (range)	107	9 (1-14)		66	9 (1-14)
CAIDE Risk Score model 2, median (range)	99	10 (1-17)		56	10 (1-15)
GM volume, ml (SD)	107	505.52 (47.93)		69	615.38 (71.16)
TIV volume, ml (SD)	107	1380.51 (129.09)		69	1339.33 (143.64)
WML volume, ml (SD)	-	-		69	32.93 (29.80)
WML visual rating, median (range)	112	5 (0-22)		-	-
MTA sum, median (range)	109	2 (0-5)		69	2 (0-6)

Values are means (± SD) for continuous variables, medians (range) for ordinal variables and absolute numbers (%) for categorical variables. Values shown for the first re-examination are weighted. Factors included in the CAIDE Dementia Risk Score were measured in midlife; others are measured in the first or second re-examinations.

Sociodemographic and clinical characteristics of the weighted CAIDE 1998 MRI population according to severity of WML are shown in Table 6.

Table 6. Sociodemographic and clinical characteristics of the weighted CAIDE MRI population in the first re-examination

Characteristic (n=112)	**No/mild WML (n=52)**	**Moderate WML (n=30)**	**Severe WML (n=30)**	**p-value**
Sex (men), %	34.6	43.3	26.7	0.399
Age in late life, yrs	71.62 (3.44)	72.90 (4.16)	74.92 (3.40)	**0.001**
Follow-up time, yrs	22.21 (2.93)	22.27 (3.95)	21.49 (2.91)	0.436
Education, yrs	6.71 (2.02)	8.23 (2.42)	7.29 (3.57)	0.162
Overweight, %	42.3	60.0	36.7	0.051
Obesity, %	19.2	6.7	36.7	0.051
Hypertension, %	53.8	40.0	73.3	**0.033**
Hypercholesterolemia, %	69.2	70.0	71.0	0.986
APOE ε4 heterozygous, %	34.6	28.6	36.0	0.562
APOE ε4 homozygous, %	5.8	10.7	0.0	0.562
Dementia, %	2.0	3.3	6.7	0.545
MCI, %	3.8	6.7	6.7	0.804
Smoking (yes), %	21.2	50.0	30.0	**0.025**
Alcohol (yes), %	34.1	45.5	36.4	0.662

Values are means (SD) for continuous variables and percents (%) for categorical variables. χ^2-test and ordinal regression were used to obtain p-value for the differences between the groups.

Subjects with moderate and severe WML were older than the subjects with no/mild WML. Midlife hypertension and overweight/obesity were more frequent in participants with more severe WML. Smoking in midlife was more common in the moderate and severe WML groups compared to no/mild WML group.

Table 7 shows the sociodemographic and clinical characteristics of the CAIDE MRI population in the second re-examination (63 individuals included in Study II) according to midlife BP levels. Subjects with midlife hypertension tended to be older than subjects without hypertension, and their BMI was significantly higher. Although the group with midlife hypertension had higher BP levels at baseline, the differences were no longer significant at the first or second re-examinations. Mean SBP levels (SD) in the entire MRI population increased from 148.52 (25.71) mmHg at midlife to 159.58 (24.26) mmHg in the first re-examination, then decreased to 147.10 (21.79) mmHg in the second re-examination. Mean DBP levels (SD) declined from 90.38 (11.44) mmHg at midlife to 84.72 (11.21) mmHg in the first re-examination and 74.92 (11.13) mmHg in the second re-examination.

Table 7. Population characteristics in the second re-examination according to the presence of midlife hypertension

Characteristic	**Controls (n=40)**	**Hypertensives (n=23)**	**p-value**
Age in the 2nd re-examination, years	77.24 (3.43)	78.76 (3.18)	0.09
Sex (men), %	40.0	34.8	0.68
Education, years	8.21 (3.08)	7.13 (1.69)	0.13
Follow-up time, years	27.65 (4.85)	28.53 (4.77)	0.49
APOE carrier status, %	40.6	36.8	0.79
SBP in midlife, mmHg	133.10 (12.47)	175.35 (20.12)	**<0.01**
SBP in the 1st re-examination*, mmHg	156.0 (22.47)	165.50 (26.47)	0.19
SBP in the 2nd re-examination, mmHg	144.63 (20.42)	151.39 (23.86)	0.24
DBP at midlife, mmHg	84.13 (6.89)	101.26 (9.49)	**<0.01**
DBP in the 1st re-examination*, mmHg	83.27 (10.95)	87.10 (11.49)	0.24
DBP in the 2nd re-examination, mmHg	74.70 (9.59)	75.30 (13.62)	0.84
Midlife BMI, kg/m^2	25.75 (3.81)	28.69 (4.57)	**0.01**
Midlife cholesterol, mmol	6.86 (0.97)	7.15 (1.35)	0.33
MMSE in the 1st re-examination*	25.64 (2.22)	25.30 (2.32)	0.61
MMSE in the 2nd re-examination	24.45 (2.28)	24.04 (2.29)	0.50
Region of Interest, mean thickness**			
Left Anterior Insula	3.92	3.66	**<0.01**
Right Anterior Insula	4.52	4.14	**<0.01**
Left Orbitofrontal Area	3.47	3.18	**<0.01**
Right Orbitofrontal Area	3.37	3.10	**<0.01**
Left PSTG***	3.16	2.90	**<0.01**
Right PSTG***	2.89	2.63	**<0.01**
Left Intraparietal Sulcus	3.29	3.06	**<0.01**
Right Temporal Pole	3.82	3.47	**<0.01**
Right Entorhinal Cortex	3.58	3.19	**<0.01**
Right Inferior Frontal Gyrus	3.20	2.95	**<0.01**

Values are means (SD) for continuous variables and percents for categorical variables. χ^2 test and independent t-test were used to obtain p-values for characteristic differences. P-values<0.05 are bold. * There were 10 subjects who did not participate in the first re-examination in 1998-1999 (3 hypertensives and 7 controls). ** Mean thicknesses (mm) were calculated for all areas that included over 50 nodes in t-statistical difference maps. Non-parametric Mann-Whitney U test was used to obtain p-value for the differences between the groups. *** PSTG = Posterior Superior Temporal Gyrus

The value of mean BMI (SD) changed from 26.84 (4.31) kg/m^2 in midlife to 29.06 (5.49) kg/m^2 in the first re-examination and 27.38 (4.71) kg/m^2 in the second re-examination. Mean cholesterol levels (SD) declined from 6.97 (1.12) mmol/l in midlife to 5.97 (1.21) mmol/l in the first re-examination, then to 5.16 (1.20) mmol/l in the second re-examination.

When the 63 subjects included in the 2005-2008 MRI population were compared to the rest of the individuals without dementia participating in the 2005-2008

differential diagnostic phase (n=108), similar patterns of change in SBP, DBP, BMI and cholesterol were observed. Significant differences between groups were observed only for DBP in 1998, with levels that were slightly lower (mean 81.00, SD 10.93 mmHg) in the CAIDE participants not included in the 2005-2008 MRI population (p=0.04).

Sociodemographic and clinical characteristics of the CAIDE MRI population in the second re-examination (69 individuals) according to history of CHD diagnosed until the first re-examination are shown in Table 8. Of the 69 participants, 59 had also attended the first CAIDE re-examination in 1998 where 49 had been cognitively normal. In all, 27 subjects fulfilled the newly suggested criteria for MCI (combining clinical with MRI findings) (Frisoni and Coleman, 2011) at the time of the second re-examination.

Table 8. Population characteristics according to history of CHD diagnosed until the 1st CAIDE re-examination

Characteristics	**no CHD (n=50)**	**CHD (n=19)**	**p-value**
Age in midlife (baseline), years	49.19 (6.21)	51.66 (5.18)	0.13
Age in 1st re-examination[a], years	70.37 (3.41)	70.89 (3.55)	0.58
Age in 2nd re-examination, years	77.78 (3.46)	78.40 (3.63)	0.51
Sex (men), n (%)	16 (32.0)	11 (57.9)	0.05
Follow-up time, years	28.59 (4.77)	26.75 (4.44)	0.15
Education, years	7.51 (2.46)	8.44 (2.90)	0.19
APOE ε4 carrier[b], n (%)	17 (40.5)	5 (33.3)	0.65
MMSE in the 1st re-examination	25.40 (2.10)	25.25 (2.70)	0.83
MMSE in the 2nd re-examination	23.90 (2.30)	24.68 (2.26)	0.21
Total GM volume, ml	617.21 (64.92)	610.54 (87.30)	0.73
Total intracranial volume, ml	1326.24 (137.20)	1375.89 (156.12)	0.20
Total WML volume, ml	31.79 (26.58)	36.23 (37.41)	0.81
Region of interest, mean cortical thickness[c], mm			
Left anterior insular cortex	4.37 (0.24)	4.06 (0.28)	**<0.01**
Right anterior insular cortex	4.21 (0.24)	3.90 (0.32)	**<0.01**
Left angular gyrus	3.18 (0.22)	2.90 (0.35)	**<0.01**
Right angular gyrus	3.18 (0.20)	2.97 (0.32)	**<0.01**
Left fusiform gyrus	3.62 (0.17)	3.42 (0.28)	**<0.01**
Right fusiform gyrus	3.43 (0.18)	3.20 (0.23)	**<0.01**
Left anterior prefrontal cortex	3.67 (0.23)	3.42 (0.29)	**<0.01**
Right anterior prefrontal cortex	3.11 (0.25)	2.88 (0.33)	**<0.01**
Left superior parietal gyrus	3.10 (0.23)	2.88 (0.29)	**<0.01**
Left superior temporal gyrus	3.21 (0.16)	2.97 (0.33)	**<0.01**
Right posterior middle frontal gyrus	3.06 (0.18)	2.82 (0.36)	**<0.01**
Right orbitofrontal area	3.77 (0.24)	3.50 (0.39)	**<0.01**
Right precentral gyrus	2.49 (0.22)	2.29 (0.24)	**<0.01**
Right inferior frontal gyrus	3.02 (0.20)	2.78 (0.34)	**<0.01**

Values are means (standard deviations) for continuous variables and numbers (%) for categorical variables. P-values <0.05 are in bold font. [a]10 subjects did not participate in the 1st re-examination; [b] APOE genotype information missing for 12 subjects; [c] Mean cortical thickness (mm) was calculated for all areas that included more than 100 nodes in t-statistical difference maps with a t-value over 3.

Only 3 participants had CHD at baseline (midlife), 19 at the time of the first CAIDE re-examination, and 26 at the second re-examination. Men tended to have CHD more often than women. No other significant differences were found between the groups with and without CHD.

5.2 BLOOD PRESSURE, BMI, AND TOTAL CHOLESTEROL FROM MIDLIFE TO LATE-LIFE IN RELATION TO WML IN LATE-LIFE (STUDY I)

Midlife hypertension was related to more severe WML 20 years later (RR 2.73; 95% CI 1.81-3.08), even after adjusting for age, sex, education, follow-up time, antihypertensive treatment, MCI/dementia diagnosis, APOE, smoking, alcohol use, total serum cholesterol, and BMI (Table 9). Further analysis revealed a significant relation between midlife DBP and late-life WML (RR 2.44; 95% CI 1.72-2.69).

People who were overweight (RR 2.53; 95% CI 1.70-2.89) or obese in midlife (RR 2.94; 95% CI 2.44-3.02) were more likely to have more severe WML in late-life, even after all adjustments.

Table 9. Midlife vascular factors and the risk of WML later in life

	RR	95% CI
Hypertension		
Model 1	2.49	**1.75-2.92**
Model 2	2.73	**1.81-3.08**
BMI 25-30		
Model 1	1.65	0.98-2.27
Model 2	2.53	**1.70-2.89**
BMI > 30		
Model 1	2.52	**1.71-2.88**
Model 2	2.94	**2.44-3.03**
Hypercholesterolemia		
Model 1	1.17	0.66-1.72
Model 2	0.85	0.20-1.90
APOE ε4 heterozygous		
Model 1	0.85	0.45-1.40
Model 2	0.70	0.28-1.41
APOE ε4 homozygous		
Model 1	1.31	0.39-2.26
Model 2	1.10	0.17-2.35

Values are RR (95% CI) from ordinal regression analyses. Model 1 is adjusted for age, sex, education, and follow-up time (hypertension analyses are also controlled for antihypertensive treatment; hypercholesterolemia analyses are also controlled for lipid-lowering treatment). Model 2 is additionally adjusted for diagnosis of dementia/MCI, APOE ε4 carrier status, midlife smoking and alcohol and other midlife vascular factors (SBP, DBP, cholesterol, BMI).

Midlife hypercholesterolemia or APOE ε4 carrier status showed no significant associations with late-life WML. In the cross-sectional analyses, only late-life overweight (RR 1.96; 95% CI 1.09-2.66) and obesity (RR 2.51; 95% CI 1.45-3.02) were related to WML after controlling for age, sex, education, MCI/dementia diagnosis, APOE, late-life smoking, alcohol use, cholesterol, SBP and DBP.

When changes in vascular risk factors over time were taken into account, hypertension was most consistently associated with more severe WML in late-life (Table 10). People with hypertension only in midlife, hypertension only in late-life, or hypertension during the entire study were more likely to have more pronounced WML as compared to people without hypertension (RR 3.25; 95% CI 2.46-3.41, RR 2.91; 95% CI 1.10-3.39 and RR 3.14; 95% CI 1.83-3.40, respectively). Antihypertensive treatment was not related to WML (RR 1.11; 95% CI 0.38-1.97).

There was also an increased risk of more severe WML in participants with BMI over 25 in both midlife and late-life (RR 2.26; 95% CI 1.42-2.62) (Table 10). Being overweight or obese in midlife only was related to a higher risk of WML (RR 2.01; 95% CI 0.71-2.62) than being overweight or obese in late-life only (RR 0.59; 95% CI 0.11-1.76), although the results were not statistically significant.

No significant relationships were found between changes in cholesterol over time and WML. However, lipid-lowering treatment decreased the risk of having more severe WML in late-life (RR 0.13; 95% CI 0.02-0.59) after adjusting for age, sex, education, follow-up time, diagnosis of dementia/MCI, APOE, midlife smoking, alcohol use and vascular risk factors (SBP, DBP, cholesterol, BMI). A total of 23 participants reported using cholesterol-lowering medication, 62 were non-users and there was no information about the remaining 27 subjects.

Table 10. Changes in vascular factors from midlife to late-life and their association with late-life WML

Blood pressure		Model 1 RR (95% CI)	Model 2 RR (95% CI)
Midlife hypertension	Late-life hypertension		
-	-	ref.	ref.
-	+	2.01 (0.65-3.08)	**2.91 (1.10-3.39)**
+	-	**3.06 (2.35-3.33)**	**3.25 (2.46-3.41)**
+	+	**2.92 (1.97-3.30)**	**3.14 (1.83-3.40)**
BMI			
Midlife > 25	Late-life > 25		
-	-	ref.	ref.
-	+	1.12 (0.24-2.65)	0.59 (0.11-1.76)
+	-	2.07 (0.68-3.16)	2.01 (0.71-2.62)
+	+	**2.18 (1.32-2.89)**	**2.26 (1.42-2.62)**
Serum total cholesterol			
Midlife hypercholesterolemia	Late-life hypercholesterolemia		
-	-	ref.	ref.
-	+	---	---
+	-	1.34 (0.60-2.04)	1.03 (0.22-2.12)
+	+	1.03 (0.37-1.87)	0.42 (0.05-1.67)

Values are RR (95% CI) from ordinal regression analyses. + is present; - is absent.

--- This category comprised only 2 subjects and could not be included in the analyses.

Model 1 is adjusted for age, sex, education, and follow-up time (hypertension analyses are also controlled for antihypertensive treatment; hypercholesterolemia analyses are also controlled for lipid-lowering treatment).

Model 2 is additionally adjusted for diagnoses of dementia/MCI, APOE ε4 carrier status, midlife smoking and alcohol and other midlife vascular factors (cholesterol and BMI in hypertension analyses; SBP, DBP and cholesterol in BMI analyses; and SBP, DBP and BMI in cholesterol analyses).

5.3 BLOOD PRESSURE, BMI AND TOTAL CHOLESTEROL FROM MIDLIFE TO LATE-LIFE IN RELATION TO CORTICAL THICKNESS IN LATE-LIFE (STUDY II)

Differences in cortical thickness between participants with and without hypertension in midlife are shown in Figure 7. The hypertension group had significantly thinner cortex in the insular and orbitofrontal areas bilaterally, the right temporal pole, entorhinal cortex, inferior frontal gyrus, intraparietal sulcus and posterior superior temporal gyri bilaterally. Similar associations were seen when lowering the BP cut-off value to 140/90 mmHg (21 controls vs. 42 hypertensives), but the differences were no longer significant. No differences in cortical thickness were found between cholesterol or BMI groups. Mean cortical thickness in the two brain regions closest to

statistical significance was 2.724 vs. 2.821 mm (medial occipital cortex) and 3.294 vs. 3.446 mm (entorhinal cortex) in the overweight (n=42) vs. control (n=21) groups, respectively. With respect to the comparison between the hypercholesterolemia (n=30) vs. control (n=33) groups, mean cortical thickness was 3.530 vs. 3.526 mm (anterior cingulate cortex), and 3.886 vs. 3.946 mm (temporal pole), respectively. The presence of at least one APOE ε4 allele was not related to cortical thickness in this population.

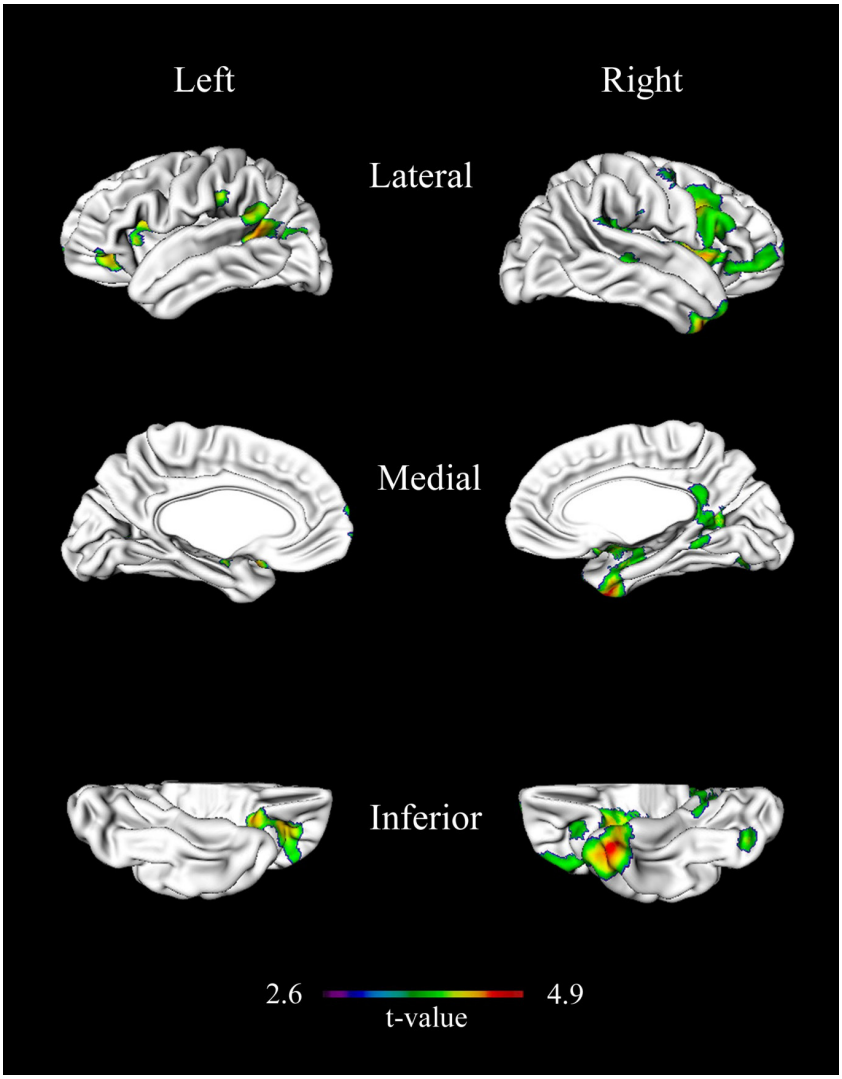


Figure 7. T-statistical difference maps for midlife hypertensives versus controls (group analysis) corrected for false discovery rate (FDR). Significant ($p<0.05$) differences in cortical thickness between groups are displayed as color-labeled t-values on the surface of a standardized brain (warmer colors indicate thinner cortex). Analysis is adjusted for age, sex, follow-up time, scanner time and antihypertensive treatment.

In linear regression analyses, higher midlife SBP levels were associated with lower cortical thickness in the anterior insular cortex bilaterally, right posterior superior temporal gyrus, right temporal pole and right inferior frontal gyrus (Table 11). Higher midlife DBP was related to thinner cortex in the posterior superior temporal gyrus bilaterally and right entorhinal cortex. Midlife PP followed a similar pattern as midlife SBP.

Table 11. Relations between midlife blood pressure values and late-life cortical thickness

Late-life cortical thickness	Midlife SBP β (p-value)	Midlife DBP β (p-value)	Midlife PP β (p-value)
AIC left	**-0.38 (0.013)**	-0.24 (0.10)	**-0.35 (0.022)**
AIC right	**-0.50 (<0.01)**	-0.22 (0.11)	**-0.51 (<0.01)**
OFC left	-0.28 (0.063)	-0.19 (0.18)	-0.24 (0.10)
OFC right	-0.22 (0.17)	-0.28 (0.057)	-0.10 (0.54)
PSTG left	-0.24 (0.095)	**-0.29 (0.031)**	-0.12 (0.39)
PSTG right	**-0.28 (0.031)**	**-0.24 (0.04)**	-0.20 (0.12)
IPS left	-0.13 (0.38)	-0.07 (0.61)	-0.13 (0.39)
TP right	**-0.33 (0.032)**	-0.16 (0.28)	**-0.33 (0.029)**
EC right	-0.31 (0.051)	**-0.31 (0.033)**	-0.19 (0.21)
IFG right	**-0.33 (0.026)**	-0.23 (0.09)	-0.28 (0.059)

Values are standardized β-coefficients (p-values) from linear regression analyses with cortical thickness as outcome variable. All analyses are adjusted for age, sex, follow-up time, scanner type, antihypertensive treatment and cardio/cerebrovascular conditions (myocardial infarction or heart failure or diabetes or stroke/transient ischemic attack). P-values<0.05 are bold.
AIC=Anterior Insular Cortex, OFC=Orbitofrontal Cortex, PSTG=Posterior Superior Temporal Gyrus, IPS=Intraparietal Sulcus, TP=Temporal Pole, EC=Entorhinal Cortex, IFG=Inferior Frontal Gyrus

There was a continuous decline in SBP from midlife until the second re-examination in subjects with cortical thickness lower than the mean in right or left anterior insular cortex (Figure 8). A similar trend was seen for SBP and right posterior superior temporal gyrus. In participants with cortical thickness higher than the mean, the decline in SBP started at older ages. SBP in midlife was higher in the group with the thinner cortex as compared with the group with higher cortical thickness ($p<0.05$), but differences in SBP between the cortical thickness groups were not significant at older ages. No differences between patterns of association with cortical thickness were observed with respect to the DBP. A relatively uniform increase in PP after midlife was observed in subjects with late-life cortical thickness lower than the mean (Figure 8). Among subjects with cortical thickness higher than the mean, PP increased until the first follow-up and then decreased. This pattern was observed for anterior insular cortex on both sides and the right posterior superior temporal gyrus. PP in midlife was higher in the group with lower cortical thickness compared with the group with higher cortical thickness in these regions ($p<0.05$), but differences in PP between cortical thickness groups were not significant at older ages.

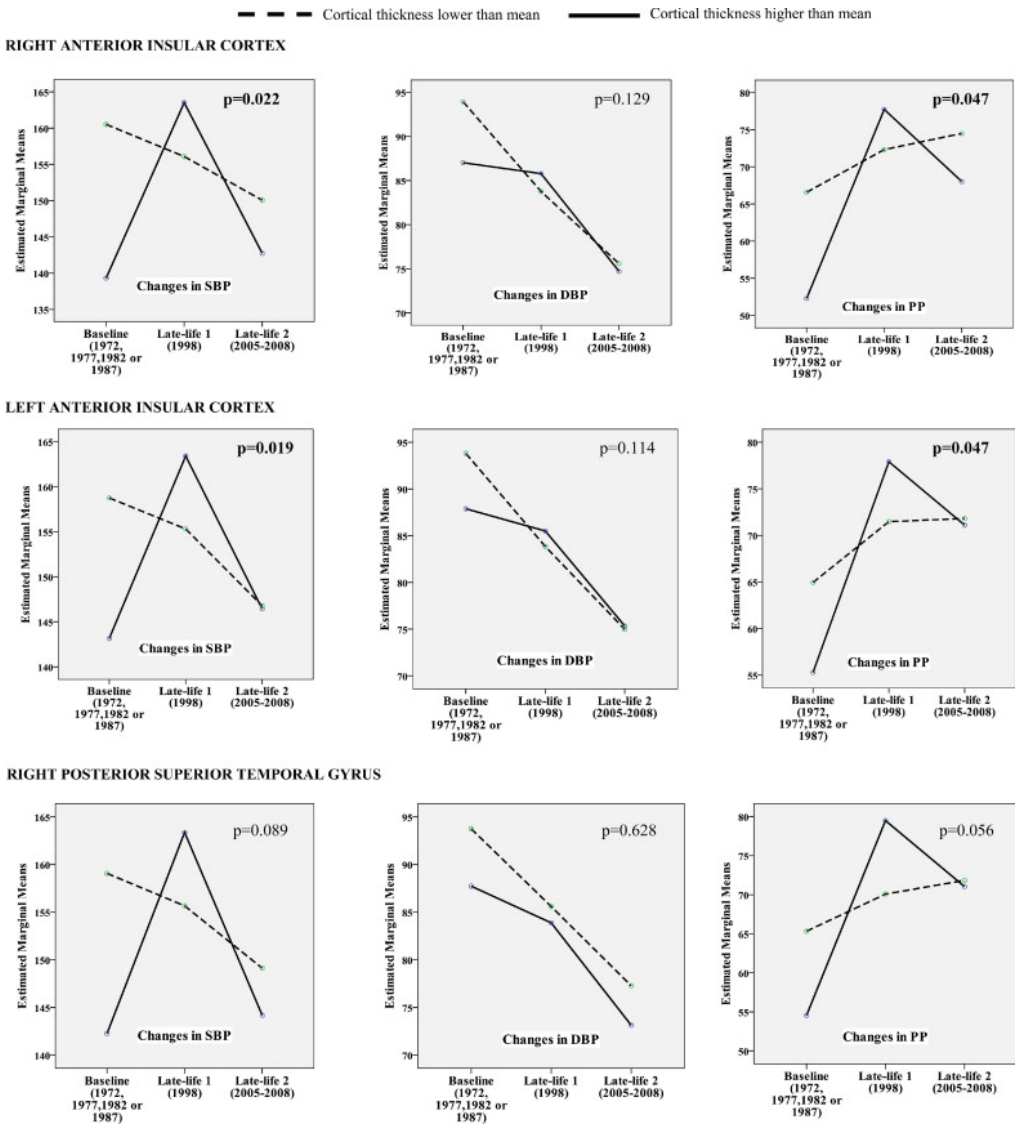


Figure 8. Changes in blood pressure from midlife to late-life in relation to cortical thickness at late-life. Y-axis shows the values of BP (SBP, DBP, PP); x-axis indicates the time of each BP measurement. The dotted line indicates changes in BP over time in people with cortical thickness lower than the mean. The continuous line indicates changes in BP over time in people with cortical thickness higher than the mean. Analyses are adjusted for age, sex, follow-up time, scanner type, antihypertensive treatment and cardio/cerebrovascular conditions (myocardial infarction or heart failure or diabetes or stroke/transient ischemic attack). P-values indicate if the patterns of BP changes are significantly different between persons with cortical thickness lower vs. higher than the mean in the second re-examination in 2005-2008.

5.4 CORONARY HEART DISEASE AND STRUCTURAL BRAIN CHANGES ON MRI (STUDY III)

Compared to participants without CHD, those with CHD diagnosed until the first CAIDE re-examination had thinner cerebral cortex in multiple areas in the MRI scans in the second re-examination 7 years later (Figure 9). The thinner cortex was observed bilaterally in the anterior insular cortex, fusiform gyrus, anterior prefrontal cortex and angular gyrus; and additionally in the left superior termporal gyrus, left superior parietal gyrus, right orbitofrontal area, right precentral gyrus, right posterior middle frontal gyrus and right inferior frontal gyrus. After additionally adjusting for midlife SBP, only three areas displayed significant differences: right posterior middle frontal gyrus, inferior temporal gyrus and fusiform gyrus. When all CHD diagnoses until the second re-examination were taken into account, a similar but non-significant relation was found between cortical thickness and CHD (results not shown). Stratification of analyses according to APOE genotype did not change the results.

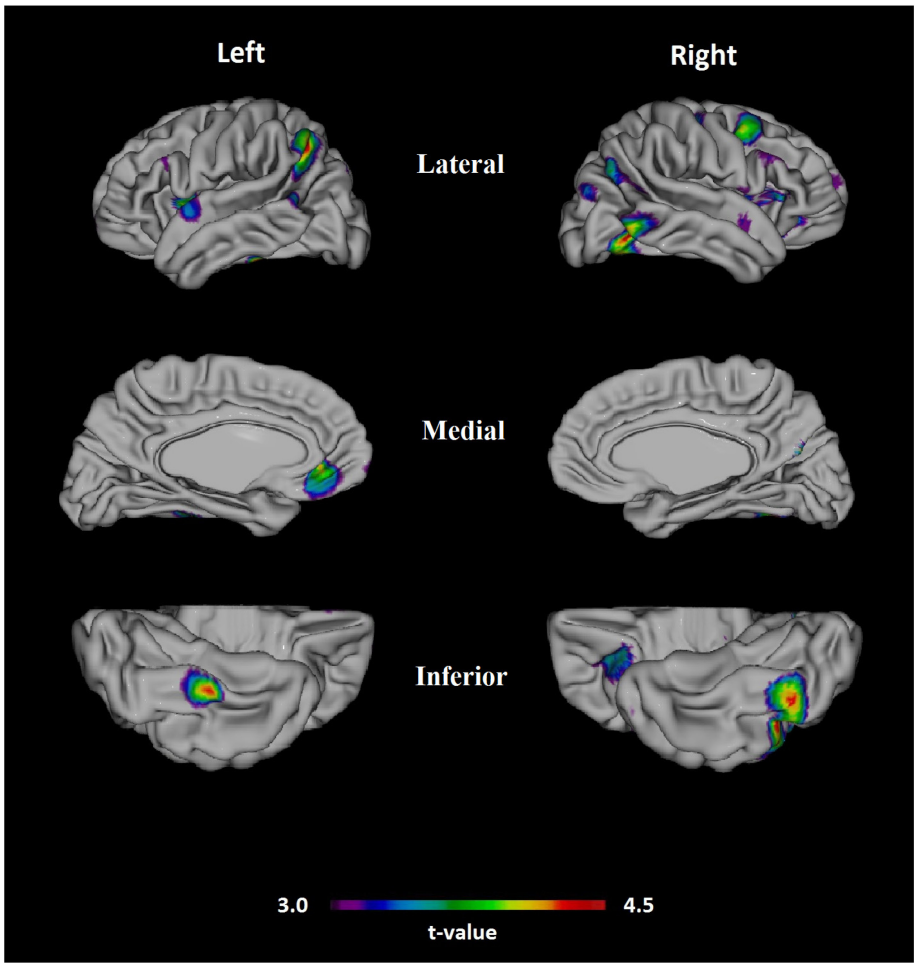


Figure 9. Statistical difference (t-value) maps of cortical thickness between CHD and control groups. Significant and FDR corrected ($p<0.05$) differences in cortical thickness between groups are displayed as color-labeled t-values on the surface of a standardized brain (warmer colors indicate thinner cortex). Analyses are adjusted for age, sex, follow-up time and scanner type.

Subjects with CHD diagnosed until the first or the second CAIDE re-examination had lower GM volume in the second re-examination: standardized β-coefficients (p-values) were -0.150 (0.018) and -0.129 (0.041), respectively. No significant associations between CHD diagnosed until the first or the second CAIDE re-examination and WML volume were found: standardized β-coefficients (p-values) were -0.046 (0.719), and 0.054 (0.670). When duration of CHD was taken into account, the associations with lower cortical thickness and GM volume were consistently significant in the group with the longer disease duration (Table 12). CHD was associated with lower cortical thickness in right anterior insular cortex and left fusiform gyrus irrespective of disease duration.

Table 12. Associations between CHD and cortical thickness, GM volume and WML volume according to the duration of CHD

MRI measurements	CHD duration ≤10 years	CHD duration >10 years
Mean cortical thickness		
• Left anterior insular cortex	-0.170 (0.139)	**-0.499 (<0.001)**
• Right anterior insular cortex	**-0.311 (0.007)**	**-0.452 (<0.001)**
• Left angular gyrus	-0.075 (0.512)	**-0.464 (<0.001)**
• Right angular gyrus	-0.165 (0.138)	**-0.417 (<0.001)**
• Left fusiform gyrus	**-0.273 (0.028)**	**-0.385 (0.002)**
• Right fusiform gyrus	-0.204 (0.094)	**-0.458 (<0.001)**
• Left anterior prefrontal cortex	-0.098 (0.407)	**-0.401 (0.001)**
• Right anterior prefrontal cortex	-0.185 (0.128)	**-0.379 (0.002)**
• Left superior parietal gyrus	-0.163 (0.174)	**-0.384 (0.002)**
• Left superior temporal gyrus	-0.153 (0.216)	**-0.340 (0.007)**
• Right posterior middle frontal gyrus	-0.193 (0.075)	**-0.481 (<0.001)**
• Right orbitofrontal area	-0.046 (0.714)	**-0.338 (0.008)**
• Right precentral gyrus	-0.167 (0.160)	**0.435 (<0.001)**
• Right inferior frontal gyrus	-0.172 (0.134)	**-0.413 (0.001)**
Total GM volume	0.002 (0.972)	**-0.191 (0.002)**
Total WML volume	0.207 (0.100)	-0.090 (0.470)

Values are standardized β-coefficients (p-values) from linear regression analyses.
All analyses are adjusted for age, sex, follow-up time and scanner type. GM volume analyses are additionally adjusted for TIV.
P-values <0.05 are bold.

Table 13 shows the effects of midlife hypertension and changes in SBP from midlife to the second re-examination on the associations between CHD and MRI measurements. The strongest relationship between CHD diagnosed until first re-examination and thinner cortex or lower GM volume in the second re-examination conducted 7 years later were found in participants with both CHD and midlife hypertension. Having CHD without midlife hypertension was also related to a reduced cortical thickness in some regions, but the associations were weaker. In participants without CHD but with midlife hypertension, total WML volume tended to be higher compared to participants with no CHD and no midlife hypertension. Subjects with CHD and whose SBP declined between midlife and second follow-up had significantly thinner cortex and lower GM volume compared to subjects with no CHD and stable SBP levels. CHD was related to a thinner cortex in some of the regions of interest even in participants with stable/increasing SBP, although the associations were weaker. A similar pattern of association was found for CHD and changes in DBP from midlife to late-life in relation to cortical thickness and GM volume in late-life. The relationship between CHD and MRI measurements was not influenced by other possible co-morbidities such as obesity and hypercholesterolemia (results not shown).

Table 13. Associations of CHD (diagnosed until the 1st CAIDE re-examination) and BP with regional cortical thickness, GM and WML volumes

MRI measurements	No CHD No midlife hypertension (N=34)	No CHD Midlife hypertension (N=16)	CHD No midlife hypertension (N=9)	CHD Midlife hypertension (N=10)		No CHD Increasing SBP (N=31)	No CHD Declining SBP (N=19)	CHD Increasing SBP (N=7)	CHD Declining SBP (N=12)
Mean cortical thickness									
Left anterior insular cortex	Ref	0.01 (0.96)	-0.17 (0.15)	**-0.54 (<0.01)**		Ref	0.03 (0.77)	-0.18 (0.13)	**-0.48 (<0.01)**
Right anterior insular cortex	Ref	-0.13 (0.21)	-0.14 (0.20)	**-0.61 (<0.01)**		Ref	-0.12 (0.27)	-0.14 (0.22)	**-0.55 (<0.01)**
Left angular gyrus	Ref	-0.13 (0.27)	*-0.23 (0.05)*	**-0.50 (<0.01)**		Ref	-0.04 (0.74)	**-0.31 (0.01)**	**-0.39 (<0.01)**
Right angular gyrus	Ref	0.04 (0.68)	-0.10 (0.35)	**-0.47 (<0.01)**		Ref	-0.05 (0.67)	-0.17 (0.16)	**-0.43 (<0.01)**
Left fusiform gyrus	Ref	0.02 (0.88)	-0.14 (0.23)	**-0.52 (<0.01)**		Ref	-0.04 (0.73)	**-0.30 (0.02)**	**-0.41 (<0.01)**
Right fusiform gyrus	Ref	-0.04 (0.70)	*-0.20 (0.08)*	**-0.62 (<0.01)**		Ref	0.01 (0.91)	*-0.22 (0.07)*	**-0.54 (<0.01)**
Left anterior prefrontal cortex	Ref	-0.06 (0.62)	**-0.24 (0.04)**	**-0.46 (<0.01)**		Ref	-0.02 (0.83)	*-0.20 (0.098)*	**-0.45 (<0.01)**
Right anterior prefrontal cortex	Ref	-0.06 (0.59)	-0.12 (0.31)	**-0.48 (<0.01)**		Ref	-0.08 (0.51)	*-0.24 (0.07)*	**-0.38 (<0.01**
Left superior parietal gyrus	Ref	0.05 (0.66)	-0.16 (0.19)	**-0.42 (<0.01)**		Ref	-0.02 (0.87)	-0.15 (0.21)	**-0.42 (<0.01)**
Left superior temporal gyrus	Ref	-0.05 (0.66)	-0.14 (0.24)	**-0.52 (<0.01)**		Ref	-0.10 (0.40)	**-0.27 (0.03)**	**-0.42 (<0.01)**
Right posterior middle frontal gyrus	Ref	-0.07 (0.52)	-0.06 (0.54)	**-0.59 (<0.01)**		Ref	*-0.21 (0.05)*	*-0.21 (0.06)*	**-0.50 (<0.01)**
Right orbitofrontal area	Ref	-0.03 (0.80)	-0.07 (0.54)	**-0.58 (<0.01)**		Ref	-0.07 (0.57)	-0.12 (0.34)	**-0.51 (<0.01)**
Right precentral gyrus	Ref	-0.03 (0.80)	-0.09 (0.42)	**-0.52 (<0.01)**		Ref	-0.13 (0.30)	-0.17 (0.17)	**-0.46 (<0.01)**
Right inferior frontal gyrus	Ref	-0.10 (0.34)	-0.07 (0.51)	**-0.54 (<0.01)**		Ref	-0.18 (0.12)	*-0.22 (0.07)*	**-0.43 (<0.01)**
Total GM volume	Ref	0.07 (0.29)	-0.03 (0.64)	**-0.16 (0.01)**		Ref	-0.04 (0.51)	-0.09 (0.16)	**-0.15 (0.02)**
Total WML volume	Ref	*0.24 (0.07)*	-0.02 (0.88)	0.06 (0.63)		Ref	0.13 (0.32)	-0.02 (0.90)	-0.01 (0.92)

Numbers are standardized beta-coefficients (p-value) from linear regression analyses.
Analyses are adjusted for age, sex, follow-up time and scanner type. GM volume analyses are additionally adjusted for TIV.
P-values <0.05 are bold and trends (p-value <0.1) are italic.

5.5 CAIDE DEMENTIA RISK SCORE AND STRUCTURAL BRAIN CHANGES ON MRI (STUDY IV)

Table 14 shows the associations between CAIDE Dementia Risk Score in midlife and MRI measurements in the first re-examination. A higher CAIDE Dementia Risk Score was associated with increased risk of having more severe WML 20 years later: RR (95% CI) was 1.69 (1.15-2.08) for the version without APOE, and 1.27 (1.00-1.67) for the version with APOE. No significant associations were found with MTA score and GM volume.

Table 14. Midlife CAIDE Dementia Risk Score and WML, MTA score and GM volume on MRI in the 1st CAIDE re-examination

	WML (visual rating) *RR (95% CI)*	**MTA score (visual rating)** *RR (95% CI)*	**GM volume** *Standardized β-coefficient (p-value)*
CAIDE Risk Score			
• <10 points (n=65)	ref.	ref.	ref.
• ≥10 points (n=42)	**1.69 (1.15-2.08)**	1.04 (0.69-1.33)	-0.03 (0.614)
CAIDE Risk Score including APOE			
• <11 points (n=57)	ref.	ref.	ref.
• ≥11 points (n=43)	**1.27 (1.00-1.67)**	1.42 (0.79-2.03)	-0.06 (0.399)

Standardized β-coefficients (p-values) are from linear regression analyses with GM volume as dependent variable. RRs (95% CIs) are from binary logistic regression analyses with WML or MTA score as dependent variable. Analyses are adjusted for follow-up time; GM volume analyses are additionally adjusted for TIV.

Table 15 shows the relations between CAIDE Dementia Risk Score and MRI measurements in the second re-examination. A risk score above 10 points (version without APOE) was related to higher WML volume (standardized β coefficient 0.27; p-value 0.036), and more severe MTA 28 years later (RR 1.91; 95% CI 1.16-2.34). These associations were not significant for the risk score version including APOE genotype. No relationship was found with GM volume.

Table 15. Midlife CAIDE Dementia Risk Score and WML volume, MTA score and GM volume on MRI in the 2nd CAIDE re-examination

	WML volume	**MTA score (visual rating)**	**GM volume**
	Standardized β-coefficient (p-value)	*RR (95% CI)*	*Standardized β-coefficient (p-value)*
CAIDE Risk Score			
• <10 points (n=41)	ref.	ref.	ref.
• ≥10 points (n=25)	**0.27 (0.036)**	**1.91 (1.16-2.34)**	0.01 (0.885)
CAIDE Risk Score including APOE			
• <11 points (n=31)	ref.	ref.	ref.
• ≥11 points (n=25)	0.21 (0.142)	1.44 (0.76-1.98)	-0.04 (0.562)

Standardized β-coefficients (p-values) are from linear regression analyses with WML volume or GM volume as dependent variables. RRs (95% CIs) are from binary logistic regression analyses with MTA score as dependent variable. Analyses are adjusted for total follow-up time and scanner type; GM volume analyses are additionally adjusted for TIV.

Comparisons of regional cortical thickness between CAIDE Dementia Risk Score groups did not pass FDR-correction (p-value<0.05), but uncorrected results (t-values from 2.5 to 3.6) suggested decreased thickness in medial temporal lobe bilaterally, right insular cortex, posterior superior temporal gyrus, and posterior cingulate gyrus in those individuals with a higher dementia risk score (results not shown).

6 Discussion

6.1 MIDLIFE BLOOD PRESSURE AND LATE-LIFE STRUCTURAL BRAIN CHANGES ON MRI

The finding of an association between midlife hypertension and more severe WML 20 years later in the CAIDE study is in line with previous longitudinal studies showing midlife hypertension as a risk factor for WML (Carmelli et al., 1999, de Leeuw et al., 1999, DeCarli et al., 1999a, Swan et al., 1998), and studies reporting increased WML progression in people with hypertension (Schmidt et al., 1999, Verhaaren et al., 2013).

The long-term effects of midlife hypertension on cortical thickness have not been previously investigated. In the CAIDE MRI population, midlife hypertension was associated with a thinner cortex up to 30 years later in several brain regions. It was decided to use a fully automatic surface-based whole brain segmentation method (Lerch and Evans, 2005) which enabled inspection of the cortex without any pre-determined ROIs. It was particularly interesting that there was an association of midlife hypertension with the insular cortex bilaterally. The insular cortex plays a crucial role in BP regulation (Nagai et al., 2010), and it is also vulnerable to changes in BP and hypoperfusion due to its location in the region of the end arterioles of the middle cerebral artery. Autoregulation of brain arterioles can normally ensure that there is sufficient blood flow to the distal parts of brain tissue regardless of BP fluctuations (Strandgaard, 1976), but chronic hypertension combined with arteriosclerosis stiffens the arteriole walls and can compromise this mechanism (Feldstein, 2012).

CAIDE participants with hypertension also had a thinner cortex in the frontal and temporal lobe. This finding is in line with a recently published systematic review focusing on BP and brain atrophy (Beauchet et al., 2013). A previous study reported an association between elevated BP in midlife and lower hippocampal volume 25 years later (Korf et al., 2004). Hypertension was not significantly related to cortical thickness in the parahippocampal gyrus in the CAIDE population, but right temporal lobe structures (temporal pole and entorhinal cortex) exhibited lower thickness in hypertensive individuals. These differences in results may be partly explained by the exclusion of images with poor cortical segmentation. It has been reported that automatic segmentation methods may have a tendency to perform poorly when there is severe medial temporal lobe atrophy (Chupin et al., 2009).

When analyzing SBP and DBP separately, only elevated midlife DBP was significantly associated with late-life WML in Study I. The relationship between midlife SBP and late-life cortical thickness was somewhat stronger than between midlife DBP and cortical thickness in Study II. Findings from earlier longitudinal

studies with over 10 year follow-up times have also been mixed. In the Honolulu-Asia Aging Study (HAAS), high midlife SBP was associated with lower brain weight at autopsy in men (Petrovitch et al., 2000). In the same study, both midlife SBP and DBP were related to hippocampal atrophy as detected with MRI (Korf et al., 2004). Lower brain volume and increased WML volume were found in twin males with elevated midlife SBP and DBP in the National Heart, Lung and Blood Institute (NHLBI) study (Carmelli et al., 1999, DeCarli et al., 1999a, Swan et al., 1998). In the Rotterdam Scan Study, elevated DBP seemed to be more strongly related than SBP to late-life brain changes (de Leeuw et al., 1999, den Heijer et al., 2012, Heijer et al., 2003). Variations in findings are even more apparent in studies with shorter follow-up times (Beauchet et al., 2013).

The association between BP and brain atrophy is complex and influenced by several factors. BP levels vary with age, and for example the increase in SBP has been postulated to last longer than the increase in DBP levels due to large-artery stiffness (Franklin et al., 1997). Gender, antihypertensive treatment, definition of hypertension, follow-up time and brain volume/pathology assessment methods are all factors that influence the results. However, longitudinal cohort studies published so far emphasize that higher levels of SBP and/or DBP are related to greater brain volume reduction (Beauchet et al., 2013). GM atrophy has also been linked to WML, although the exact mechanisms are unknown (Appelman et al., 2009). Strategically situated WM changes might lead to deafferentation of connections between sub-cortical and cortical structures and ultimately cause subsequent cortical atrophy. Also Wallerian degeneration (Waller, 1850) is one possible explanation, but histological verification of this theory is still lacking (Pantoni and Garcia, 1997).

6.2 CHANGES IN BLOOD PRESSURE FROM MIDLIFE TO LATE-LIFE AND LATE-LIFE STRUCTURAL BRAIN CHANGES ON MRI

Compared to participants without hypertension, those who developed hypertension later in life, and those with long-standing hypertension from midlife to late-life were more likely to have more severe WML. The strongest association with WML was seen for declining BP (hypertension in midlife but not in late-life). A similar relation between declining BP over a 20 year period and WML was reported in Rotterdam Scan Study; interestingly, this pattern was not observed in participants with shorter 5-years of follow-up (de Leeuw et al., 1999). The Rotterdam Scan Study also indicated that DBP decreased from midlife to late-life in individuals with increased late-life brain atrophy (Heijer et al., 2003).

In the CAIDE study, declining SBP and increasing PP during three decades after midlife were associated with thinner cortex in brain areas involved in BP regulation (e.g. insula). SBP also decreased in subjects with thicker cortex, but it started later as compared to subjects with thinner cortex. This may be due to a bidirectional relationship between BP and brain changes: midlife hypertension increases the risk

of cerebrovascular or Alzheimer lesions/atrophy in the insular cortex, and once such lesions occur, they may affect BP regulation and lead to a decline in BP. In a previous study, subjects with elevated casual BP in 24-h ambulatory measurements had more insular subcortical hyperintensities as compared to controls (Goldstein et al., 2005). In autopsy studies, increased intracerebral accumulation of AD pathology was found in individuals with midlife hypertension (Petrovitch et al., 2000), and NFT pathology has been reported to affect insular cortex already in the preclinical phase of AD (Braak et al., 1998). The CAIDE 2005-2008 MRI population consisted of elderly subjects at-risk of dementia, and a pattern of decline in BP has been described in the years before the onset of dementia (Qiu et al., 2009). Declining BP and increased PP in midlife may also be related to cardiovascular diseases (Banach and Aronow, 2012), which are risk factors for dementia and cognitive impairment (Bunch et al., 2010, Qiu et al., 2006, Ross et al., 1999). However, adjustments for cardiovascular conditions and antihypertensive treatment did not change the results in Study II, suggesting that the BP decline may be related to lower cortical thickness independently of these other cardiovascular factors.

6.3 BMI FROM MIDLIFE TO LATE-LIFE AND LATE-LIFE STRUCTURAL BRAIN CHANGES ON MRI

Both obesity (BMI >30 kg/m^2) and overweight (BMI 25-30 kg/m^2) in midlife increased the risk of more severe WML two decades later in the CAIDE MRI population. A previous longitudinal study focusing on older people reported that every increase in BMI of 1.0 at age 70 doubled the risk of WML approximately 18 years later in elderly women (Gustafson et al., 2004). Other cross-sectional studies in middle-aged individuals have linked adiposity to WM pathology (Gazdzinski et al., 2008, Yamashiro et al., 2014). Signs of myelin damage were also reported in younger people who were overweight (Mueller et al., 2011, Verstynen et al., 2012). However, these studies had small sample sizes and no adjustments were made for BP. Cross-sectional findings from the Framingham study have indicated that there is a relation between increased SBP and decreased WM integrity already in early midlife (Maillard et al., 2012), and BP levels need to be taken into account.

Midlife adiposity has been related to increased dementia risk (Kivipelto et al., 2005, Whitmer et al., 2005a). As with BP, there is also a pattern of decline in BMI over time in individuals who will develop dementia later (Atti et al., 2008, Nourhashemi et al., 2003). In Study I, reduction in BMI values after midlife tended to relate to more severe WML in late-life, although the association was not statistically significant. However, elevated BMI during 20 years from midlife significantly increased the risk of more severe WML.

Individuals who are overweight/obese tend to have other comorbidities such as hypertension, hypercholesterolemia or diabetes, making it more difficult to study the independent effect of a single risk factor. Adiposity has been speculated to increase

the level of inflammation (Trayhurn and Wood, 2005), and levels of C-reactive protein have been associated with more severe and progressive WML in elderly people (van Dijk et al., 2005). A recent cross-sectional DTI-study indicated that the link between adiposity and white matter integrity is at least partly mediated via inflammation-related processes (Bettcher et al., 2013). Obesity has also been reported to exert an independent effect on carotid artery wall thickening in middle aged women (De Michele et al., 2002), which may lead to effects on the progression of cerebral arteriolosclerosis. Obstructive sleep apnea (OSA) is a frequent comorbidity accompanying adiposity, and OSA-induced night-time hypoxia, hypercapnia and transient hypertension episodes may be detrimental to the brain. Previous studies have related OSA to an increased risk of cognitive impairment and dementia (Yaffe et al., 2011), and also to GM and WM changes (Macey et al., 2002, Macey et al., 2008, Morrell et al., 2003).

6.4 CHOLESTEROL FROM MIDLIFE TO LATE-LIFE AND LATE-LIFE STRUCTURAL BRAIN CHANGES ON MRI

In the CAIDE 1998 MRI population, lipid-lowering drugs seemed to be protective against more severe WML. However, serum total cholesterol levels were not associated with WML or cortical thickness. Theoretically, hypercholesterolemia-induced atherosclerosis could affect cerebral arterioles, leading to GM and WM changes. Cholesterol levels have also been associated with Alzheimer pathology (Björkhem et al., 2009, Launer et al., 2001. However, previous studies focusing on serum cholesterol levels and GM or WM changes have produced conflicting results (den Heijer et al., 2005a, Koschack et al., 2009, Leritz et al., 2011, Wolf et al., 2004). Only total serum cholesterol levels were measured at midlife in the CAIDE study. Guidelines for the prevention and treatment of CHD and ischemic stroke emphasize the importance of LDL and HDL in the development of atherosclerosis (Catapano et al., 2011). The levels of LDL- and HDL-cholesterol will also need to be taken into account when evaluating the effects of cholesterol on brain changes.

6.5 CORONARY HEART DISEASE AND STRUCTURAL BRAIN CHANGES

CHD was associated with decreased cortical thickness and lower total GM volume, and this relation was particularly strong for CHD with a longer duration (at least 10 years). A previous cross-sectional study in male twins linked CHD to lower total GM volume (DeCarli et al., 1999b), but other studies have failed to detect this kind of association (Geerlings et al., 2010, Koschack and Irle, 2005, Manolio et al., 1994). The decline in brain volume observed in patients with CHD has been previously reported in regions related to AD such as temporal lobe, posterior cingulate and precuneus (Almeida et al., 2008, Koschack and Irle, 2005). In Study III, a similar

association between CHD and thinner cortex in parietal lobe structures was observed. Other regions related to cognitive functions, such as fusiform gyrus (Han et al., 2012, Tijms et al., 2013) and prefrontal cortex (Funahashi, 2001), also had a lower thickness in the CHD group.

Individuals with CHD often have other co-morbidities such as hypertension, hypercholesterolemia or other cardiovascular diseases. Similarly to CHD, hypertension-related brain changes are more frequently observed in the frontal lobe (Beauchet et al., 2013, Maillard et al., 2012). Cortical thinning and total GM volume loss were most evident in CAIDE participants with both CHD and midlife hypertension, pointing to a combined effect of these two factors. Furthermore, subjects with CHD and a declining SBP displayed more pronounced cortical thinning and lower total GM volume, a pattern similar to that observed in Study II. Declining BP values could also be a marker of left ventricular dysfunction, which can occur as a consequence of myocardial ischemia. Only four subjects with CHD had been diagnosed with heart failure in the CAIDE 2005-2008 MRI population, and adjusting the analyses for HF did not change the results. No quantitative measures of ventricular function (e.g. ejection fraction) were available, so milder forms of heart failure could not be identified. After adjusting for midlife hypertension in the analyses of the relationship between CHD and cortical thickness, some regions still showed significant associations, suggesting that the effects of CHD on the brain may be partly independent of BP.

Other cardiac diseases such as heart failure and atrial fibrillation may also increase the risk of dementia (Bunch et al., 2010, Miyasaka et al., 2007, Qiu et al., 2006). Studies of heart failure, atrial fibrillation and structural brain changes have reported less conflicting results in comparison to studies focusing on the relation between CHD and brain changes (Almeida et al., 2012, de Leeuw et al., 2000, Stefansdottir et al., 2013, Vogels et al., 2007). CHD and hypertension are both well known risk factors for heart failure and atrial fibrillation, which may in turn contribute to brain atrophy (Roman, 2004, Stefansdottir et al., 2013). These associations could not be studied in the CAIDE MRI populations due to the small number of participants with these distinct disorders (4 with heart failure and 5 with atrial fibrillation).

CHD diagnoses in the Finnish Hospital Discharge Register represent CHD severe enough to require hospitalization and there for milder forms of CHD could not be identified. In addition, people with severe CHD are less likely to survive to older ages, and thus the findings from Study III may actually underestimate the effects of CHD on the brain.

APOE ε4 has been associated with higher risk of CHD (Bennet et al., 2007) and also with more severe coronary atherosclerosis (Kosunen et al., 1995). However, the APOE genotype did not influence the association between CHD and MRI measurements in Study III, possibly due to lack of statistical power.

6.6 CAIDE DEMENTIA RISK SCORE AND STRUCTURAL BRAIN CHANGES

CAIDE Dementia Risk Score is a validated tool for estimating the 20 to 40 year dementia risk in the general population based on a midlife risk profile, but it was previously unclear if its dementia prediction ability relies more on cerebrovascular than on neurodegenerative pathology. A higher CAIDE Dementia Risk Score in midlife was associated with more severe WML 20 to 30 years later. An association with more pronounced MTA was observed in the population with longer follow-up times. Individuals with higher CAIDE Dementia Risk Score tended to have thinner cortex in several regions (e.g. posterior cingulate gyrus, temporal lobe, insular cortex), but these results did not remain after correction for multiple comparisons. There was no relation with total GM volume.

Since the risk score is based largely on vascular factors previously linked to WM and GM changes (Carmelli et al., 1999, de Leeuw et al., 1999, Gustafson et al., 2004, Gustafson et al., 2004, Korf et al., 2004, Soreca et al., 2009), it is not surprising that both more severe WML and MTA were found in individuals with higher midlife CAIDE Dementia Risk Score. Cerebrovascular lesions can be present in AD, especially at older ages, and they can lower the threshold for dementia (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study, 2001, Snowdon et al., 1997). Hippocampal atrophy is a characteristic feature of AD (Burton et al., 2009), but it can also be present in VaD (Jack et al., 2002, Shiino et al., 2012, Yin et al., 2014). Previously, interactions between vascular and Alzheimer pathology have been described (Niwa et al., 2000, Thal et al., 2008).

A higher dementia risk score in midlife was associated with both visually rated WML in the first CAIDE re-examination and WML volume in the second re-examination. Interestingly, more pronounced MTA was seen only in participants with higher risk scores in midlife and with longer follow-up times (i.e. second CAIDE re-examination). MTA is one of the diagnostic and early markers of AD (Dubois et al., 2007, Jack et al., 2013), and it has been pathologically characterized by an elevated NFT burden (Braak and Braak, 1991, Polvikoski et al., 2010). While WML may be common in the general population even at younger ages (Launer, 2004), MTA may take longer time to develop. The associations between midlife CAIDE Dementia Risk Score and cortical thickness in the second re-examination were not significant after correction for multiple comparisons, but it is worth noting that the principal identified regions (posterior cingulate gyrus, temporal lobe, and insular cortex) follow previously reported brain atrophy patterns in AD (Lerch et al., 2005).

In the initial publication, adding APOE ε4 carrier status to the CAIDE Dementia Risk Score did not significantly improve the scale's ability to predict dementia (Kivipelto et al., 2006). In Study IV, the risk score version including APOE was related to more severe visually rated WML in the first CAIDE re-examination, but not to the other MRI outcomes in the first or second re-examination. Since information about APOE genotype was not available for all participants, this may be

at least partly due to limited statistical power. Some previously postulated midlife risk factors for dementia such as diabetes mellitus, depressed mood, head trauma, central obesity, lung function or smoking are not included in the original CAIDE Dementia Risk Score, but in a recent study adding these factors into the analysis did not increase dementia prediction accuracy (Exalto et al., 2013).

6.7 METHODOLOGICAL CONSIDERATIONS

The four studies included in this thesis are based on data from the longitudinal population-based CAIDE study. CAIDE is one of the few studies with available detailed health-related information already at midlife, two re-examinations with total follow-up time of up to 30 years, and which has been specifically designed to investigate risk factors for dementia and AD.

One of the main limitations of Studies I-IV is the relatively small sample size, reducing their statistical power. This may have led to an underestimation or even a failure to observe the associations (type II error) between vascular risk factors/conditions and the MRI measurements. Small sample size also limited the possibility to do comprehensive stratified analyses based on participants' cognitive status. The CAIDE MRI populations include selected individuals who participated in the first or second re-examination. In the CAIDE 1998 MRI population (39 individuals with dementia, 31 with MCI and 42 controls, age- and sex-matched), data weighting was used to achieve representativeness with the original CAIDE sample. This was not possible in the 2005-2008 MRI population (37 dementia, 70 MCI and 6 controls). Instead, the analyses focused on participants at risk of dementia, and those already with dementia were excluded. Including a high proportion of people with dementia would have affected the results for two main reasons: manifest dementia involves rather pronounced brain changes, with the risk of misidentification/overestimation of associations with vascular factors; and pronounced brain abnormalities can also affect the quality of the automatic segmentation of MRIs. The 69 participants at risk of dementia in the 2005-2008 CAIDE MRI population were not significantly different from the rest of the individuals in the original CAIDE population with respect to age at baseline ($p=0.3$), gender ($p=0.8$), education ($p=0.2$), midlife SBP ($p=0.2$) or DBP ($p=0.6$), total cholesterol ($p=0.09$), BMI ($p=0.8$), physical activity ($p=0.4$), APOE genotype ($p=0.7$), or CHD diagnosed during the study ($p=0.4$).

Although MRI was performed in both re-examinations, only 18 subjects had MRI from both time points. It was thus not possible to analyze changes in MRI measurements over time in relation to vascular factors. The MRI acquisition parameters and scanners were also different in the first and second re-examinations, limiting image analysis in some cases (e.g. WML volume and cortical thickness could not be measured reliably on some images from the first re-examination).

Non-participation and survival bias may have also influenced the results. Individuals in the original CAIDE target population who died or did not participate in re-examinations had poorer health status and higher vascular risk (e.g. higher BP, BMI and cholesterol) compared to survivors/participants (Kulmala et al., 2014). This may have led to an underestimation of the effects of vascular risk factors on the brain.

Cognitive testing and MRI were not available at the baseline (midlife) visit. Alzheimer and cerebrovascular pathologies can start to develop long before any dementia diagnosis, and the possibility of reverse causality needs to be taken into account. However, if there were some individuals exhibiting the early stages of dementia (and more pronounced brain pathology) already at baseline, they would have been unlikely to survive and participate in re-examinations. Potential GM atrophy or WML in participants who later on developed dementia would nor have been anticipated to be severe enough to have a major influence on BP levels at midlife (Dickerson et al., 2011, Jack et al., 2013).

The CAIDE study provided a large amount of information about vascular and lifestyle-related factors, and analyses in Studies I-IV took into account several potential confounders and effect mediators. This is particularly important as vascular risk factors may affect the brain through shared pathways, and they can also interact with each other. However, the possibility of residual confounding cannot be fully excluded (e.g. less severe comorbid cardiovascular conditions who did not require hospitalization).

7 Conclusions

Based on the findings from the present set of studies, the following conclusions can be drawn:

1) Midlife hypertension was associated with an increased risk of more severe WML and lower cortical thickness 20 to 30 years later. Individuals with longstanding hypertension and those who developed hypertension at older ages also had an increased risk of WML. A decline in blood pressure from midlife to late-life was observed in subjects with thinner cortex in brain areas involved in blood pressure regulation (e.g. insular cortex).

2) The presence of midlife overweight and obesity were related to an increased risk of more severe WML 20 years later. Elevated BMI from midlife to late-life was associated with WML in late-life.

3) Although the serum total cholesterol level was not related to brain MRI measurements, lipid-lowering treatment seemed to exert a protective effect against WML.

4) Lower total GM volume and reduced cortical thickness in several brain regions were found in subjects with coronary heart disease, particularly in those with a longer disease duration. This association was influenced by midlife blood pressure levels and changes in blood pressure over time.

5) Higher midlife CAIDE Dementia Risk Score was associated with more severe WML and MTA 20 to 30 years later.

The results of this project emphasize that vascular risk factors and conditions existing from midlife to older ages can influence the structural brain changes detected later with MRI. A longer exposure time to such factors is particularly detrimental. A validated, easy to use risk score for estimating dementia risk based on vascular factors can also point to an increased risk for cerebrovascular and neurodegenerative changes, and could be useful for identifying at-risk individuals who may benefit most from preventive interventions.

8 Future Perspectives

Evidence from observational studies supports the hypothesis that there is an association between vascular risk factors already in midlife and late-life cognitive impairment, creating a window of opportunity for prevention. Interestingly, recent studies have hinted that the incidence of dementia may be indeed declining (Matthews et al., 2013, Qiu et al., 2013, Schrijvers et al., 2012). One possible explanation for this phenomenon is that there have been changes in cardiovascular risk factors since the 1960s-1970s, i.e. decreasing prevalence of hypertension, hyperlipidemia or smoking. However, both overweight and DM are becoming more common in middle-aged and older populations (Fielding et al., 2013, Finucane et al., 2011, Luchsinger, 2010, Vartiainen et al., 2010). The midlife assessment of CAIDE participants took place during a time when the levels of many vascular risk factors were generally high throughout Eastern Finland (Puska et al., 1979). New epidemiological studies are needed to confirm the trend of declining dementia incidence, and also to investigate vascular risk factors in the new generations of older people, since it is clear that conditions in the population can change significantly during the time when long-term follow-up studies are on-going. It also remains to be determined whether changes in dementia incidence are accompanied by changes in the type and severity of brain pathology.

Although observational studies have indicated that treatment of vascular factors (e.g. antihypertensive treatment, lipid-lowering medication) may decrease the risk of dementia and slow cognitive decline (Chang-Quan et al., 2011, Deschaintre et al., 2009, Luchsinger et al., 2007, Rockwood et al., 2002), these promising findings have not been easily translated into successful dementia prevention in randomized controlled trials (RCT) (Ligthart et al., 2010, Richard et al., 2012b). However, these RCTs were often add-on studies in trials focusing on decreasing cardiovascular mortality and preventing cardio- or cerebrovascular events. They also tended to include younger populations (<70 years), which resulted in a relatively low incidence of dementia and cognitive impairment, and thus they had a limited power to detect significant treatment effects (Ligthart et al., 2010). These methodological issues will need to be addressed in future prevention RCTs.

Future RCTs focusing on prevention of cognitive decline would be advised to include biomarkers for dementia-related diseases (e.g. MRI, PET or CSF markers) in order to better assess the overall effects of the intervention. Antihypertensive treatment has been postulated to exert a beneficial effect on WML progression in observational studies (Godin et al., 2011, Verhaaren et al., 2013), but no change in GM atrophy was seen in a 1-year follow-up study despite successful antihypertensive treatment (Jennings et al., 2011). In a 2-year RCT, statin therapy slowed the progression of WML in the group with severe WML already at baseline

compared to the control group (Mok et al., 2009), but these results have not been confirmed in other RCTs (ten Dam et al., 2005).

Late-life cognitive impairment is a heterogeneous condition and focusing only on treating a single risk factor may not be enough. RCTs targeting several risk factors simultaneously may be more likely to represent effective prevention strategies. Such multi-domain RCTs are already ongoing in several European countries, e.g. the European Dementia Prevention Initiative (EDPI, http://www.edpi.org) (Dehnel 2013, Richard et al., 2012). The EDPI includes three RCTs already in progress: in Finland, the Finnish Geriatric Intervention study to prevent cognitive impairment and disability (FINGER) (Kivipelto et al., 2013); in the Netherlands, the Prevention of Dementia by Intensive Vascular Care (preDIVA) trial (Richard et al., 2009); and in France, the Multidomain Alzheimer Prevention Trial (MAPT) (Carrié et al., 2012). Cognitive functioning or dementia are the primary outcomes in these trials, and they also include several neuroimaging exploratory outcomes: basic structural MRI modalities, and additionally DTI, FDG-PET for brain glucose metabolism, and PiB-PET for brain amyloid are used in sub-groups in FINGER and MAPT. FINGER, MAPT and preDIVA have intervention periods of 2, 3 and 6 years, respectively, and planned follow-up periods of 7, 5 and 6 years (Richard et al., 2012a). Since brain changes on structural MRI and FDG-PET can be seen already years before AD/dementia (Jack et al., 2013), the results concerning the effects of vascular and lifestyle preventive interventions on these biomarkers will be of high interest.

A fourth trial, Healthy Aging Through Internet Counselling in the Elderly (HATICE) (http://www.hatice.eu/), focusing on management of vascular risk factors and conditions, is planned to start in 2015 in the Netherlands, Finland and France.

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Miika Vuorinen

Cardiovascular Risk Factors and Dementia-related Structural Brain Changes on MRI

A 30-year Follow-up Study

Vascular risk factors and conditions have been associated with dementia and Alzheimer's disease (AD), but the mechanisms are not fully understood. Because typical Alzheimer and cerebrovascular pathologies can develop long before dementia onset, a life-course perspective is needed to investigate risk factors. The present thesis focused on the effects of vascular risk factors and conditions during three decades from midlife to late-life on dementia-related structural brain changes on MRI in late-life.

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