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Minna Rusanen

Smoking, Pulmonary and Heart Diseases and the Risk of Cognitive Impairment and Dementia: An Epidemiological Approach

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ABSTRACT

As more people are surviving into more advanced ages, prevention of dementia is now a major public health challenge. Data on several cardiovascular and lifestyle related factors as a risk factor for dementia have been accumulating during the recent years. The present thesis focuses on putative risk factors for dementia and its major cause, Alzheimer's disease (AD), and cognitive impairment that have not been previously indepth studied: smoking and common pulmonary and heart diseases. The project aimed to add to the current knowledge on the complex puzzle of risk factors of AD.

Three studies (study I, III and IV) of the present thesis are based on the Finnish Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study. CAIDE is a population-based study investigating cardiovascular and lifestyle related risk factors for dementia and cognitive functioning. Participants (n=2000) were derived from independent, random, population-based samples studied in 1972, 1977, 1982, or 1987. Re-examinations of the cohort have been carried out in 1998 and in 2005-2008. Altogether 1511 (75.6 %) individuals participated in the re-examinations. Study II was based on a retrospective cohort (n= 21 123) of members of the Kaiser Permanente Medical Care Program of Northern California. The participants were examined once at midlife, and dementia diagnoses were ascertained from electronic medical record database on average 23 years later.

This series of studies showed that smoking in midlife increases the risk of dementia and its major subtypes, AD and vascular dementia, later in life. The risk may be especially pronounced among persons carrying one susceptibility gene to AD, apolipoprotein E (APOE) ε4. The presence of two common pulmonary diseases, chronic obstructive pulmonary disease (COPD) and asthma, at midlife were also associated with an increased risk of cognitive impairment in late-life. However, pulmonary diseases not diagnosed until late-life were inversely associated with cognitive impairment. Heart diseases are common among the elderly, and this study indicates that especially atrial fibrillation in late-life may increase the subsequent risk of dementia and AD. Heart diseases diagnosed already in midlife did not increase the risks, except among the APOE ε4 carriers with heart failure who were at an increased risk of AD.

The present set of results provide another reason for quitting smoking or never starting the habit, and also suggest that prevention and treatment of pulmonary and heart diseases may be important also from the perspective of brain health and cognitive functioning. The current data improve our understanding that dementia results from many, partly modifiable, risk factors, not all of which necessarily affecting directly the brain itself.

National Library of Medical Classification: WT 155, WT 150, WM 220, WL 358.5, WA 105
Medical Subject Headings: Dementia; Alzheimer Disease; Mild Cognitive Impairment;
Epidemiology; Risk Factors; Smoking; Lung Diseases; Heart Diseases; Apolipoprotein E4

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TIIVISTELMÄ

Väestön ikääntyessä dementiaa sairastavien henkilöiden määrä tulee kasvamaan räjähdysmäisesti, ja tämän uhkakuvan valossa dementian ennaltaehkäisyllä on nyt ja tulevaisuudessa erittäin merkittävä kansanterveydellinen ja -taloudellinen merkitys. Tähän mennessä on löydetty vain joitakin dementian riskitekijöitä, joihin voidaan aikaisella hoidolla tai ennaltaehkäisevällä työllä vaikuttaa. Tämän väitöskirjatyön tarkoituksena oli selvittää tupakoinnin sekä yleisten keuhko- ja sydänsairauksien vaikutusta kognitiivisen heikentymisen ja dementian kehittymiseen.

Kolme osatutkimusta (I, III ja IV) pohjautuvat suomalaiseen Kardiovaskulaariset riskitekijät, ikääntyminen ja dementia (CAIDE) tutkimukseen. CAIDE –tutkimuksen (n=2000) osallistujat on poimittu satunnaisesti Pohjois-Karjala projektin ja FINMONICA tutkimuksen neljään itsenäiseen väestöotokseen vuosina 1972, 1977, 1982 ja 1988 osallistuneista henkilöistä. Yli 20 seurantavuoden jälkeen 1511 (75.6 %) henkilöä osallistui CAIDE –tutkimuksen seurantakäynneille vuosina 1998 ja 2005-2008. Väitöskirjan toinen osatutkimus pohjautuu yhdysvaltalaiseen retrospektiiviseen, monietniseen tutkimuskohorttiin (Kaiser Permanente of Northern California). Henkilöt (n=21 123) osallistuivat vuosina 1978-1985 vapaaehtoiseen terveystarkastukseen ja keskimäärin 23 seurantavuoden jälkeen sähköisestä sairauskertomusjärjestelmästä selvitettiin kuinka moni oli sairastunut dementiaan.

Tutkimus osoitti, että tupakointi keski-iässä lisää myöhempää riskiä sairastua dementian yleisimpiin muotoihin Alzheimerin tautiin (AT) ja verisuoniperäiseen dementiaan. Riski oli erityisen suuri henkilöillä, joilla on perimässään AT:n yleinen riskigeeni apolipoproteiini E (APOE) ε4. Myös keski-iässä diagnosoitu keuhkoahtaumatauti ja astma olivat yhteydessä myöhempään kognitiiviseen heikentymiseen. Sairastuminen näihin keuhkosairauksiin vasta myöhemmällä iällä oli käänteisesti yhteydessä kognitiiviseen heikentymiseen. Lisäksi tutkimus osoitti, että ikääntyvien yleiset sydänsairaudet, erityisesti eteisvärinä, lisäävät myös riskiä sairastua dementiaan ja AT:iin. Kuitenkin jos sydänsairaus oli todettu jo keski-iässä, ainoastaan sydämen vajaatoiminta APOE ε4 –kantajilla oli yhteydessä myöhempään AT:n riskiin.

Tulokset osoittavat, että tupakoinnin välttäminen sekä keuhko- ja sydänsairauksien hyvä hoito saattaa ehkäistä dementiaa. Vaikuttaa todennäköiseltä, että geneettisten ja elämäntapatekijöiden lisäksi myös muut sairaudet vaikuttavat dementiariskiin, ja näiden hyvä hoito yhdistettynä terveisiin elämäntapoihin voi auttaa dementian ehkäisyssä.

Luokitus: WT 155, WT 150, WM 220, WL 358.5, WA 105
Yleinen suomalainen asiasanasto: dementia; Alzheimerin tauti; muistisairaudet; epidemiologia; riskitekijät; tupakointi; keuhkosairaudet; sydäntaudit; apolipoproteiinit

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Joensuu, January 2013

Minna Rusanen

List of the original publications

This dissertation is based on the following original publications:

I Rusanen M, Rovio S, Ngandu T, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Midlife Smoking, Apolipoprotein E and Risk of Dementia and Alzheimer's Disease: a Population-Based Cardiovascular Risk Factors, Aging and Dementia Study. *Dementia and Geriatric Cognitive Disorders, 30:277-284, 2010.*

II Rusanen M, Kivipelto M, Quesenberry C, Zhou J, Whitmer R. Heavy Smoking in Midlife and Long-term Risk of Alzheimer Disease and Vascular Dementia. *Archives of Internal Medicine, 171:333-339, 2011.*

III Rusanen M, Ngandu T, Laatikainen T, Tuomilehto J, Soininen H, Kivipelto M. Chronic Obstructive Pulmonary Disease and Asthma and the Risk of Mild Cognitive Impairment and Dementia: a Population-Based CAIDE Study. Submitted for publication.

IV Rusanen M, Kivipelto M, Levälahti E, Laatikainen T, Tuomilehto J, Soininen H, Ngandu T. Heart Diseases and Long-term Risk of Dementia and Alzheimer's Disease: a Population-Based CAIDE Study. Submitted for publication.

Contents

Abbreviations

AACD	Aging-associated cognitive decline
AAMI	Age-associated memory impairment
Aβ	β-amyloid
AD	Alzheimer's disease
ADDTC	Alzheimer's Disease Diagnostic and Treatment Center
ADRDA	Alzheimer's Disease and Related Disorders Association
AF	Atrial fibrillation
AIREN	Association Internationale pour la Recherche et l'Enseignement en Neurosciences
AP	Angina pectoris
APOE	Apolipoprotein E
APP	Amyloid precursor protein
BMI	Body mass index
CASI	Cognitive Abilities Screening Instrument
CBD	Corticobasal degeneration
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHD	Coronary heart disease
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
CSN	Canadian Stroke Network
CT	Computer tomography
CVD	Cerebrovascular disease
DBP	Diastolic blood pressure
DLB	Dementia with Lewy bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
FAD	Familiar Alzheimer's disease
FEV1	Forced expiratory volume in 1 second
FTLD	Frontotemporal lobar degeneration
FVC	Forced vital capacity
HAAS	Honolulu-Asia Aging Study
HF	Heart failure
HIS	Hachinski Ischemic Scale
ICD	International Classification of Diseases
MCADRC	Mayo Clinic Alzheimer's Disease Research Center
MCI	Mild cognitive impairment
MI	Myocardial infarction

MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangles
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NINDS	National Institute of Neurological Disorders and Stroke
PAD	Peripheral artery disease
PDD	Parkinson's disease dementia
PEF	Peak expiratory flow
PET	Positron emission tomography
PS	Presenilin
PSP	Progressive supranuclear palsy
SBD	Systolic blood pressure
SPECT	Single-photon emission computed tomography
VaD	Vascular dementia
VCI	Vascular cognitive impairment
WHO	World Health Organization

1 Introduction

Thanks to the previous and ongoing epidemiological studies, the big picture illustrating the risk factors and development of dementia and Alzheimer's disease (AD) has become clearer during recent years. A specific challenge in Alzheimer research is that AD has a very long preclinical phase with a progressive disease pathology development in the brain which goes on for even decades before the first clinical symptoms appear (Braak et al. 1999, Ohm et al. 1995). Risk factors measured in midlife may better predict dementia in late-life because they are less affected by the disease process. Therefore long, detailed epidemiological studies which investigate the putative risk factors for dementia and AD already in midlife are crucial in identifying the constitutive risk factors which may trigger the onset as well as contributing to the development of the disease. In this way, it will be possible to understand more comprehensively the pathophysiological mechanisms of this complex disease, and furthermore, in the future hopefully prevent or at least delay its onset. In view of the increasing longevity of populations worldwide, prevention of dementia has turned into a major public health challenge. The current study is an overview of the risk factors of dementia and AD and cognitive impairment focusing on three major issues not previously widely studied: a very common lifestyle related risk factor smoking and major comorbid pulmonary (chronic obstructive pulmonary disease (COPD) and asthma) and heart diseases (atrial fibrillation (AF), heart failure (HF), and coronary heart disease (CHD)). The study aimed to contribute to the current knowledge on the complex puzzle of risk factors of AD.

2 Review of the literature

2.1 MEMORY DISORDERS

2.1.1 Dementia

Dementia is a syndrome causing deterioration in memory and, in addition, deficits in other cognitive functions including aphasia, apraxia, agnosia or disturbances in executive functioning. The most disturbing symptom is sustainable and usually progressive worsening of memory functions. The cognitive decline must be severe enough to cause impairment in social or occupational functioning causing a decline from the persons' previous level of functioning (American Psychiatric Association 1994). Dementia is a syndrome with many underlying causes, the most common being AD; others include vascular dementia (VaD), frontotemporal lobar degenerations (FTLD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), and other more rare etiologies (e.g. alcohol related dementia, HIV-related dementia, Creutzfeldt–Jakob disease). The main focus of this thesis is on dementia in general, and on AD and VaD, which will be discussed in detail, while other causes of dementia will be only briefly described.

Nowadays the most widely used diagnostic criteria for dementia are those defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association 1994) and the World Health Organization's (WHO) International Classification of Diseases, 10th Revision (ICD-10) (World Health Organization 2004). There have also been other criteria in use especially in the past, but not all of these will define the same persons as being demented and this must be taken into account while reviewing dementia research (Erkinjuntti et al. 1997). The upcoming 5th edition of DSM (DSM-V), which is going to be published in May 2013, emphasizes the different ethiologies of dementia, and in the updated version dementia and other cognitive disorders are actually categorised as neurocognitive disorders rather than dementia.

The most obvious risk factor for dementia is advanced age, and accordingly, the occurrence of dementia nearly doubles every 5 years after the age of 65 years. The estimated prevalence of total dementia among persons aged 65 to 69 years was 0.8 % in one European pooled study, while over one out of every fourth individual over 90 years has been estimated to be demented (Lobo et al. 2000). In 2005, the overall global prevalence of dementia among persons ≥ 60 years was estimated to be 3.9 % (> 24 million people) according to an international expert panel (Ferri et al. 2005). The World Alzheimer Report 2009 by Alzheimer's Disease International (ADI) estimated that in 2010 a total of 35.6 million people worldwide are living with dementia (available at homepage of ADI: http://www.alz.co.uk/research/files/WorldAlzheimerReport.pdf). Moreover, if dementia prevention efforts fail then the figures are estimated to continue increasing considerably in the next few decades (Wimo et al. 2003). This represents a huge social as well as economical burden to society. The worldwide societal costs of dementia have increased by 34 % in the few years between 2005 and 2009 (Wimo et al. 2010). Consequently, finding effective preventive strategies for dementia should be one of the top priorities in public health politics worldwide.

2.1.2 Alzheimer's disease

Alzheimer's disease is nowadays regarded as the most important cause of dementia. It is estimated to account for between 50 to 70 % of all dementia cases (Lobo et al. 2000, Fratiglioni et al. 2000a). After Alois Alzheimer in 1906 first described the symptoms of Auguste D, a 51-year-old

woman with progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence, the disease was long considered as a rarity (Maurer et al. 1997). At autopsy of Aguste D, there were plaques, neurofibrillary tangles, and arteriosclerotic changes found in her brain. It was not until the 1970's that it was discovered that these histopathological features are very commonly found in the brains of demented persons (Blessed et al. 1968).

The pathophysiology of AD is not yet completely understood. However, AD is histopathologically characterized by the formation of extracellular amyloid plaques and intraneuronal neurofibrillary tangles (NFT) in the brain, resulting in neuronal dysfunction and cell death (Braak et al. 1995, Delacourte et al. 1999). The amyloid plaques are products of sequential proteolytic cleaving process of the amyloid precursor protein (APP), an integral membrane protein found in many tissues and concentrated in the synapses of neurons. APP cleaving process can be carried out by 3 enzymes; the α-, β- and γ-secretases. The cleavage by β- and γ-secretase results in the formation of 38- to 43-amino-acid β-amyloid (Aβ) peptides. The longer Aβ peptides ($A\beta_{42}$), which represent about 10% of all Aβ species in the brain, display an increased tendency to aggregate and accumulate as extracellular amyloid deposits in senile plaques (Vetrivel et al. 2006). Aβ aggregates are also found in the walls of cerebral blood vessels causing amyloid angiopathy. On the contrary, the nonamyloidogenic cleavage process of APP by α-secretase has been found to be neuroprotective. In AD, the balance of APP processing in the brain is in favour of the amyloidogenic pathway. Some investigators have suggested that the oligomeric forms of Aβ may actually be more synaptotoxic than the Aβ plaques, these in fact may serve as a protective mechanism against the oligomeric species (Shankar et al. 2008). The second histopathological hallmark of AD is the formation of intracellular NFT's. NFT's are the result of hyperphosphorylation of the microtubule associated protein, Tau, leading to its oligomerization, and microtubule destabilization within the cell, and ultimately, to apoptosis of the neuron (Avila 2006). These characteristic histopathological changes can first be found in the medial temporal lobe structures (including entorhinal cortex and hippocampus) and subsequently during disease progression also the neocortex becomes widely affected, and the progression of the changes takes place in a very hierarchical manner (Braak et al. 1995, Delacourte et al. 1999). As a result, there is marked neuronal loss and consequently brain atrophy seen especially in the temporal lobe structures, and later during the disease course, also cortical and central atrophy is evident (Cras et al. 1995). However, neither hyperphosphorylation of tau nor amyloid plaque formation are exclusively found in AD. There are also other neurodegenerative diseases, referred as to tauopathies, which are characterised by intraneuronal filamentous deposits consisting of hyperphosphorylated tau (e.g. frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD)) (Goedert et al. 2005). There are also some amyloid plaques, usually called diffuse plaques, formed during normal aging in the brain, but histopathologically they are somewhat different from the neuritic plaques commonly seen in AD. Moreover, clinically diagnosed probable AD is considered to be a pathologically heterogenous disorder with many persons exhibiting mixed pathologies (Schneider et al. 2009).

The current diagnosis of AD is based on the typical clinical picture and specific supportive findings in clinical examination. There are several guidelines for diagnosing AD, including the DSM-IV and the ICD-10. However, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) work group clinical criteria for the diagnosis of AD published in 1984 (McKhann et al. 1984) are most widely used in research. They are well validated and provide a sufficient diagnostic accuracy of 85 to 90 % in diagnosing probable AD (Gearing et al.

1995). The core of the symptoms is a progressive impairment in episodic memory. According to the NINCDS-ADRDA criteria, the diagnosis of probable AD include 1) dementia established by clinical examination and documented by a standard test of cognitive functions and confirmed by neuropsychological tests, 2) deficits in two or more areas of cognition, 3) progressive worsening of memory and other cognitive functions, 4) no disturbance of consciousness, 5) onset between ages 40 and 90, typically after 65, and 6) absence of other systemic or brain disorder that would account for the symptoms. In addition, the diagnosis is supported by a progressive deterioration of specific cognitive functions including aphasia, apraxia, and agnosia, impaired activities of daily living, family history of AD, and normal laboratory assessments. Features that do not support the diagnosis include a sudden onset of symptoms, focal neurological symptoms, seizures, and gait disturbances very early in the course of the disease. The diagnosis of definite AD requires that the clinical criteria for probable AD are fulfilled, and in addition, that there is histopathological evidence obtained on autopsy. The Neuropathology Task Force of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) in 1991 published a standardized neuropathology protocol for the postmortem assessment of dementia in order to refine the diagnostic criteria of AD (Mirra et al. 1991).

A need to revise the diagnostic criteria of AD has emerged from the better understanding of clinical phenotype and advances in knowledge of the biological basis of AD, and furthermore, the recognition of distinctive biological markers of AD. There is also a desperate need to develop early intervention strategies for the prevention of AD. Since it is known that the disease process starts to evolve in the brain years before the first clinical symptoms appear, there is an explicit need for a protocol which could diagnose AD as early as possible, even before the first symptoms. Interventions with disease-modifying therapies would be expected to be more effective, and more precisely targeted against the putative neuropathological mechanisms, when conducted earlier in the disease course. Subsequently, when extensive neuronal loss and brain atrophy are already present, the effect of interventions may be much more limited. Recent advances in neuroimaging, cerebrospinal fluid (CSF) assays, and other biomarkers now provide the ability to detect evidence of the AD pathophysiological process in vivo. The major AD biomarkers that have been widely investigated at this time may be divided into two classes based on the biological processes which they measure (McKhann et al. 2011). Biomarkers of β-amyloid protein deposition are low CSF levels of $A\beta_{42}$ and positive positron emission tomography (PET) amyloid imaging. The second category includes biomarkers of downstream neuronal degeneration or injury. The three major biomarkers in this category are elevated levels in CSF tau (both total tau and phosphorylated tau), decreased 18-fluorodeoxyglucose uptake on PET in temporo–parietal cortex, and disproportionate atrophy on structural magnetic resonance imaging (MRI) in medial, basal, and lateral temporal lobe, and medial parietal cortex. It has been hypothesized that the earliest detectable pathological change in the brain of an individual with AD is Aβ accumulation (Sperling et al. 2011). However, some investigators have proposed that synaptic, mitochondrial, metabolic, inflammatory, neuronal, cytoskeletal, and other age-related alterations may play an even earlier, or more central, role than Aβ in the pathogenesis of AD (Pimplikar et al. 2010). An elevated CSF tau level is not specific to AD and is thought to be a later biomarker of neuronal injury, accompanied by synaptic depletion and neuronal loss (Sperling et al. 2011). Later during the disease course, neurodegenerative changes related to AD become visually detectable as brain atrophy in structural MRI. However, the association between the pathological features of AD and clinical dementia may depend on the age; the association is believed to be stronger in younger old persons than in older old persons (Savva et al. 2009). Thus, age must be taken into account when assessing the effect of interventions against AD.

With the accumulation of new knowledge, the diagnosis of AD is no longer merely a diagnosis of exclusion. A revision of the NINCDS-ADRDA criteria for establishing new research criteria for the diagnosis of AD was published in 2007 (Dubois et al. 2007). These criteria emphasize the significance of these new biomarkers for AD. In order to meet the criteria for probable AD, the individual must have: 1) early and significant episodic memory impairment as a core symptom and 2) one or more of the supportive biomarker criteria, i.e. the presence of medial temporal lobe atrophy in MRI, an abnormal CSF biomarker (low $A\beta_{42}$, increased total tau or increased phospho-tau concentration, or combinations of these three), a specific pattern on functional neuroimaging with PET, and a proven AD autosomal dominant mutation within the immediate family. In addition, the diagnosis of definite AD does not necessarily require neuropathological confirmation on autopsy, but can also be made in the presence of clinical evidence together with histopathological evidence of the disease in brain biopsy or genetic evidence (mutation in chromosome 1, 14 or 21). Another revision of the NINCDS-ADRDA criteria by an international workgroup convened by National Institute on Aging and the Alzheimer's Association has also been published in 2011 (McKhann et al. 2011). According to these criteria, in individuals who meet the core clinical criteria for probable AD dementia, the biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. However, the AD biomarker tests are not proposed for routine diagnostic purposes at the present time.

Sporadic AD is by far the most common form of AD. However, there is also a particular class of AD, familiar AD (FAD), which needs to be discussed here. At the present, FAD has been linked to mutations in three genes: APP, PS-1 (presenilin-1) and PS-2 (presenilin-2) located in chromosomes 21, 14 and 1, respectively. However, it has been speculated that additional susceptibility genes exist (Bertram et al. 2004). The identified genes are responsible for the expression of the proteins APP, PS-1 and PS-2. APP is the precursor protein of Aβ, and PS-1 and PS-2 are components of a protein complex that is involved in the cleavage of APP to form Aβ. Thus, the accumulation and aggregation of Aβ may be augmented by mutations in these genes, resulting in very early Aβ formation in the brain. The clinical picture in FAD is the same as that encountered in sporadic AD, but the symptoms start very early, usually around 40 to 50 years of age. Compared to sporadic AD, FAD is rare; it accounts for only 5 % of all AD cases.

2.1.3 Vascular dementia

The second most common form of dementia is VaD, constituting approximately 15 to 20 % of all dementia cases. There are several guidelines for diagnosing VaD, including the criteria defined in the DSM and ICD coding systems, and Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) (Chui et al. 1992), and Hachinski Ischemic Scale (HIS) (Hachinski et al. 1975) criteria. In 1993, the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) convened an International Workshop with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) and published research criteria for the diagnosis of VaD (Roman et al. 1993). These guidelines emphasize: 1) the heterogeneity of vascular dementia syndromes and pathologic subtypes including ischemic and hemorrhagic strokes, cerebral hypoxic-ischemic events, and senile leukoencephalopathic lesions, 2) the variability in the clinical course of the disease, which may be static, remitting, or progressive, 3) specific clinical findings early in the disease course (e.g. gait disorder, incontinence, or mood and personality changes) that support a vascular rather than a degenerative cause, 4) the need to establish a temporal relationship between stroke and dementia onset for a secure diagnosis, 5) the importance of brain imaging to support clinical findings, 6) the value of

neuropsychological testing to document impairments in multiple cognitive domains, and 7) the value of using a protocol for neuropathologic evaluations and correlative studies of clinical, radiologic, and neuropsychological features. These criteria were created especially for the purpose of case definition in epidemiologic studies. As evaluated neuropathologically, the sensitivity of the criteria is estimated to be 58 % and specificity 80 % in one study of 113 autopsied elderly patients with dementia (Gold et al. 1997). Thus, in particular, the sensitivity of the criteria is rather low. Furthermore, the diagnostic criteria for VaD in different coding systems differ considerably in their abilities to identify VaD patients; in one study with a series of patients with poststroke dementia, the number of cases that could be classified as VaD varied between 32 to 91 % according to the different criteria used in that study (DSM-III, ADDTC, NINDS-AIREN, ICD-10, DSM-IV) (Pohjasvaara et al. 2000). A recent review has suggested that the NINDS-AIREN criteria are the most specific and useful criteria in research, but the different criteria proposed for vascular dementia are not interchangeable (Wiederkehr et al. 2008).

A clear differentiation of AD and VaD may be clinically difficult in some cases, especially when extensive ischemic white matter lesions accompany an otherwise typical clinical picture of AD. In fact, it is recognized that especially among elderly persons, neurodegenerative and vascular neuropathology often co-exist and "mixed" dementia or AD with cerebrovascular disease (CVD) might actually be the most common form of dementia among persons of advanced age (Kalaria 2002). "Mixed" dementia is rarely diagnosed in the clinic, however, as the majority of diagnostic procedures are biased toward a diagnosis of AD, and in fact, significant CVD and stroke have generally been considered as an exclusion criteria for the clinical diagnosis of AD. Furthermore, the definition of dementia specifies memory impairment as an essential feature of the disease. This definition identifies patients with AD, but often misses the executive dysfunction typical of cognitive disorders due to vascular causes. Thus, the emphasis of VaD research has shifted towards the concept of vascular cognitive impairment (VCI). VCI is considered as the modern term related to vascular burden of the brain, reflecting all the encompassing effects of CVD on cognition. VCI includes all levels of cognitive decline from milder deficits up to outright dementia. In an attempt to identify and describe those individuals with cognitive impairment related to vascular factors, or VCI, in 2006 NINDS and Canadian Stroke Network (CSN) published their vascular cognitive impairment harmonization standards (Hachinski et al. 2006). One important reason for developing these criteria was that VCI patients who are not yet demented are better candidates for participating in clinical trials because they are at earlier stages of their illness. Since vascular risk factors (e.g. hypertension, high cholesterol, and diabetes) are treatable, it has been postulated that early treatment should prevent, postpone, or mitigate VCI as well as the possible vascular exacerbation of AD. Furthermore, since AD and VaD or VCI also share many of the same risk factors, they both must be considered as a focus of future research and the knowledge on the pathophysiological mechanisms leading to these conditions must be further expanded.

2.1.4 Other dementias

Other more rare, but clinically relevant, forms of dementia include dementia with Lewy bodies (DLB) (McKeith et al. 2005), Parkinson's disease dementia (PDD) (Emre et al. 2007), and frontotemporal lobar degenerations (FTLD) (McKhann et al. 2001). It has been proposed that DLB is the second most common type of degenerative dementia in the elderly, possibly accounting for up to 15 to 25 % of all dementia cases in autopsy samples (McKeith et al. 1996). Clinically, DLB is characterized by progressive cognitive impairment, leading to dementia with fluctuating cognition, recurrent detailed visual hallucinations, and parkinsonism (McKeith et al. 2005).

Attention deficits and problems in executive functions and visuospatial performance usually occur early in the disease course and are prominent. The major histological feature of DLB is the presence of neuronal inclusion bodies called Lewy bodies in subcortical and cortical areas. Lewy bodies consist mainly of insoluble aggregates of α-synuclein protein associated with other proteins such as ubiquitin. However, there is a pronounced neuropathological and clinical overlap with AD as well as with PDD. In PD, Lewy bodies are found in the substantia nigra, and if progressing to PDD, they are usually also found widespread in the cortex (Tsuboi et al. 2007). In fact, DLB and PDD have been speculated to represent two clinical entities on the spectrum of Lewy body disease. Many patients with DLB also have AD neuropathology, i.e., cortical amyloid plaques and also to a lesser extent neurofibrillary tangles. Conversely, Lewy bodies are also frequently found in cases of AD, including patients with both sporadic AD and FAD (Hamilton 2000). Thus, DLB can coexist with AD.

FTLD comprises a heterogeneous group of syndromes defined clinically by early and progressive changes in behaviour and personality and/or in language (McKhann et al. 2001). Memory and other cognitive functions in contrast to language are relatively well preserved until the late stages of the disease. These disorders are especially important in the differential diagnostics of early onset dementia because the symptoms usually affect individuals younger than 65 to 70 years. Neuropathologically, FTLD is attributable to a neurodegeneration in the frontal and/or temporal lobes. The histopathological findings vary considerably from tau-positive and ubiquitin-positive inclusions to those lacking any distinct histopathological features apart from frontotemporal neuronal loss and gliosis.

There are still a number of other disorders which can cause dementia (e.g. dementia due to the neurodegenerative diseases multisystem atrophy (MSA), PSP and CBD, Huntington's disease, Creutzfeldt–Jakob disease, HIV-related dementia and dementia due to normal pressure hydrocephalus), but they are very rare and will not be discussed in detail here, because the focus of this thesis is on dementia as a whole and specifically on AD and VaD.

2.1.5 Mild cognitive impairment

A subtle cognitive decline can precede the more distinctive symptoms of AD by many years. This has established the need for defining the clinical entity preceding dementia. During the last decades, there have been many definitions of the mild changes occurring in elderly cognition, starting from the 1950's term "benign senescent forgetfulness" introduced by the Czech-Canadian psychiatrist and neurologist V. A. Kral (Kral 1962). During the 1980's and 1990's the terms "age-associated memory impairment" (AAMI) and "aging-associated cognitive decline" (AACD) (Levy 1994) were the first which contained specific clinical criteria. However, mild cognitive impairment (MCI) is nowadays the most frequently used term. MCI is proposed to be a transitional state between normal aging and dementia. However, it is known to be a heterogeneous state in terms of clinical presentation, etiology, and prognosis (Mariani et al. 2007). The rate of conversion of MCI to dementia varies among studies, but is estimated to be approximately 4 to 11 % per year (Panza et al. 2005). It is also known that several cognitive functions may decline with normal aging without any underlying neurodegenerative disease and with no progression towards dementia, (Christensen 2001, Christensen et al. 1999) and moreover, some of those persons diagnosed with MCI may even revert back to normal cognitive functioning. Thus, differentiating between the predromal stage of dementia and the stable MCI or cognitive decline related to normal aging is still a challenging task, nonetheless the clinical data on MCI have increased enormously during recent years and huge efforts have been made in better defining this clinical entity.

The criteria of MCI proposed by the Mayo Clinic Alzheimer's Disease Research Center (MCADRC) have been widely used during recent years in many studies, especially in clinical trials on MCI (Smith et al. 1996, Petersen et al. 1995). The criteria include: 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 one other area of cognitive function as evidenced by scores > 1.5 standard deviation (SD) below the age-appropriate mean, 5) Clinical Dementia Rating (CDR) score of 0.5, and 6) absence of dementia. New consensus criteria for MCI have also been introduced by an international expert panel (Winblad et al. 2004). The content of these criteria is essentially the same as those previously suggested by the MCADRC, but these allow for minimal impairment of complex instrumental functions along with preserved activities of daily living. Furthermore, after establishing that an individual person has MCI, the clinical presentation may be classified according to three subtypes: amnestic, multiple domain (with or without a memory component), and single nonmemory domain (e.g. executive functions, language, visuospatial skills). A similar classification has also been proposed by another international group of experts in order to emphasize the multiple clinical presentations and underlying etiologies of MCI (Petersen et al. 2001). However, a substantial body of evidence suggests that MCI, especially its amnestic form, largely represents predromal AD (Dubois et al. 2004). Subjects diagnosed with MCI are estimated to convert to AD at a rate of 10 to 12 % per year (Petersen et al. 1999). Consequently, a diagnosis of MCI has been recognized as marking an individual as suitable candidate for possible therapeutic intervention.

2.2 RISK AND PROTECTIVE FACTORS

In recent years several factors have been examined in relation to the risk of dementia and AD. There is a growing body of evidence indicating that the development of dementia is a result of interaction between genetic susceptibility and environmental factors. The current evidence on risk or protective factors for dementia and AD has been summarized in two recent reports, one by the National Institutes of Health (NIH) (Williams et al. 2010) and other by the Swedish Council on Health Technology Assessment (SBU) (available at homepage of SBU: http://www.sbu.se/upload/Publikationer/Content1/1/Dementia_vol1.pdf). Table 1 presents a summarized overview of these main putative risk or protective factors. They consist of a mixture of modifiable as well as non-modifiable risk factors. As illustrated in Table 1, various lifestyle related, modifiable factors have been linked to the disease risk. Moderate or high evidence for the association has been reported for apolipoprotein E (APOE) ε4 allele, familial aggregation, high blood pressure and high cholesterol at midlife, diabetes, low education, physical activity, and anti-hypertensive drugs. The evidence regarding the other factors is still regarded as less convincing. The present work gives a brief overview of the main identified risk and protective factors. A detailed review is presented on the risk factors that are of central interest in this thesis, specifically: smoking, pulmonary diseases and heart diseases.

Table 1. The main examined risk and protective factors for dementia and AD

	RISK FACTORS	PROTECTIVE FACTORS
DEMENTIA		
	APOE ε4 allele	Anti-hypertensive drugs
	Familial aggregation	Physical activity
	High blood pressure	Moderate alcohol use
	Diabetes	Social network
	Low education	Mediterranean diet
	Smoking	Statins
	Obesity	Hormone replacement therapy?
	High homocysteine levels	Non-steroidal anti-inflammatory drugs?
	Cardiovascular disease	
	Cerebrovascular disease	
	Inflammation markers	
	Folate/B12-vitamin deficiency	
	Depression	
	Low socio-economic status	
	Head trauma	
ALZHEIMER'S DISEASE		
	APOE ε4 allele	Physical activity
	Familial aggregation	Moderate alcohol use
	High blood pressure	Social network
	High cholesterol levels	Mediterranean diet
	Diabetes	Statins
	Low education	Hormone replacement therapy?
	Smoking	Non-steroidal anti-inflammatory drugs?
	Obesity	
	High homocysteine levels	
	Cardiovascular disease	
	Cerebrovascular disease	
	Inflammation markers	
	Folate/B12-vitamin deficiency	
	Depression	
	Low socio-economic status	
	Head trauma	

2.2.1 Sociodemographic and socioeconomic risk factors

Age and family history were the first established risk factors for sporadic dementia and AD. The most obvious risk factor for dementia is advanced age. Both the incidence and prevalence of dementia increase in conjunction with aging; the occurrence nearly doubles every 5 years after the age of 65 years (Lobo et al. 2000). Those individuals who have at least one first degree relative with dementia are at an increased risk of developing dementia compared to persons without a family history, and this effect has also been shown to exist among various ethnic croups (van Duijn et al. 1991, Devi et al. 2000). Ethnic group may influence the overall occurrence of dementia; higher rates of dementia have been reported among African-American and Latino populations than in non-Latino Whites (Gurland et al. 1999). Gender may also affect the disease risk; women are known to display an increased risk especially of developing AD compared to men (Fratiglioni et al. 2000a, Launer et al. 1999). A higher risk of dementia and AD has also been linked with low educational level (Launer et al. 1999, Ott et al. 1995, Anttila et al. 2002). Lower socio-economic status may also predict the risk of developing AD (Evans et al. 1997).

2.2.2 Modifiable risk factors

Many lifestyle related and environmental factors have recently been linked to the risk of dementia and AD. These have evoked a great deal of interest, as many of these factors are easily modifiable. Obesity is usually caused by poor nutrition and low physical activity, and it is nowadays one of the major public health problems in the Western countries. It constitutes a major risk factor for vascular diseases, and is also one of the most important actual causes of death in the United States (Mokdad et al. 2004). Obesity especially in midlife has been linked to an increased risk of dementia and AD in several studies (Kivipelto et al. 2005, Whitmer et al. 2005, Kalmijn et al. 2000). A diet rich in saturated fats may increase the risk of dementia and AD irrespective of the BMI value, whereas moderate intake of unsaturated fats may be protective (Laitinen et al. 2006, Morris et al. 2003). Moderate alcohol drinking has also been shown to be protective of dementia while frequent alcohol drinking may predispose to the disease (Anttila et al. 2004, Ruitenberg et al. 2002). Regular physical activity (Rovio et al. 2005, Laurin et al. 2001) as well as a rich social network (Fratiglioni et al. 2000b), being married (Hakansson et al. 2009, Helmer et al. 1999), and social and mental activities (Wang et al. 2002) have all been associated with a reduction on the risk of dementia and AD.

Many established risk factors for vascular diseases have also been linked to an increased risk of dementia and AD. Hypertension is a well-recognised risk factor for stroke and coronary heart disease (CHD). Recently, several population-based studies have demonstrated that elevated blood pressure in midlife can also increase the risk of dementia and AD in late-life (Whitmer et al. 2005, Kivipelto et al. 2001, Launer et al. 2000). However, interestingly, a decline in blood pressure is seen in the years preceding the diagnosis of dementia (Skoog et al. 1996, Qiu et al. 2004). This low blood pressure has actually been speculated as being an accelerating factor in the neurodegenerative process in the brain after the appearance of neurodegenerative lesions in strategic cerebral locations regulating blood pressure have first initiated the decline. Indeed, a lower blood pressure has been detected in the demented individuals than in their non-demented counterparts (Guo et al. 1996). A similar association has been detected between serum cholesterol values and dementia risk; i.e. high cholesterol in midlife has been shown to increase the risk of dementia and AD (Whitmer et al. 2005, Kivipelto et al. 2001, Notkola et al. 1998), but a decline in cholesterol after midlife is observed in those individuals who will develop dementia in late-life (Notkola et al. 1998, Solomon et al. 2007). It has been speculated that the reduction in the cholesterol level may reflect the ongoing neurodegenerative disease process in the brain, and it may even represent a risk marker for late-life cognitive impairment. However, the relationships between these factors are complex and may also at least partly reflect phenomena related to physiological aging and also changes in lifestyle (such as diet, physical activity, or smoking). There is also evidence that diabetes mellitus may contribute to the development of dementia and AD (Ott et al. 1999, Peila et al. 2002, Xu et al. 2004). There are many mechanisms through which diabetes has been postulated to influence the risk of dementia, including the toxic impact of hyperglycemia, the appearance of insulin resistance, the presence of oxidative stress, advanced glycation endproducts, inflammatory cytokines, and vascular mechanisms. Interestingly, individuals with diabetes have been shown to display more vascular lesions and less AD-related neuropathology in the brain in post-mortem autopsy, and it may be that fewer neuropathologic lesions are needed to evoke dementia in these persons with cerebrovascular lesions (Ahtiluoto et al. 2010). Furthermore, these vascular risk factors often occur simultaneously (defined as the metabolic syndrome), and the clustering of these vascular risk factors has been shown to additively increase the risk of dementia (Whitmer et al. 2005, Kivipelto

et al. 2001, Luchsinger et al. 2005). Subsequently, the question has risen if anti-hypertensive drugs, statin treatment for hypercholesterolemia, and diabetes medication can decrease the risk of developing dementia and AD. There is some evidence that antihypertensive treatment (Poon 2008) and statins (Pac-Soo et al. 2011) may be beneficial in preventing dementia, but the results have been far from consistent. However, the present understanding that vascular factors seem to have an impact on the disease process already starting from midlife stresses the importance of long-term treatment of these risk factors already starting at least from midlife. Likewise, further research is needed on the association of these factors with dementia and the treatment of the risk factors starting already from midlife to obtain the ultimate answers about the role of these factors in the development of the disease.

2.2.3 The apolipoprotein E ε4 allele

Thus far APOE ε4 allele is the only established susceptibility gene for sporadic or late-onset AD. It has been estimated that it accounts for about 60 % of the genetic component of late-onset AD (Rubinsztein et al. 1999). The APOE gene located in chromosome 19 has 3 common alleles: ε2, ε3, and ε4, corresponding to 6 different phenotypes. In typical Caucasian populations, the most common allele is ε3 with ε2 being the most infrequent; the average frequencies of ε2, ε3 and ε4 are 8 %, 75 % and 15 %, respectively (Davignon et al. 1988). Moreover, some variations in the frequency of the alleles have been reported in different populations (Corbo et al. 1999). In Finland and Scandinavia, the proportion of APOE ε4 carriers in the population is known to be somewhat greater than in some other European countries (on average 15 %) (Schiele et al. 2000, Ehnholm et al. 1986). In the Finnish Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study, more than 30 % of the study population were found to carry at least one ε4 allele, thus, the occurrence of the ε4 allele in that study can be considered as high. There is also evidence that the effect of the ε4 may vary in different ethnic groups; ε4 may be weaker risk factor for AD among African Americans and Hispanics than in Caucasians and Japanese (Farrer et al. 1997). In addition to AD, the APOE ε4 carriers have an increased risk of several diseases including cardiovascular disease, cerebrovascular disease, and neurodegenerative disorders including LBD (Smith 2000). The ε4 allele has also been linked to increased mortality (Ewbank 2004); however, results concerning the effect of APOE ε4 on survival are contradictory. In one population-based study,the APOE phenotype or AD did not influence mortality in the aged population (Koivisto et al. 2000). Once AD had become manifest, APOE ε4 alone did not influence survival. However, in subjects with AD not carrying APOE ε4, men had reduced survival compared to women.

APOE carries out multiple functions in the brain and different alleles have specific properties. The protein produced by the APOE gene is an important component of many types of plasma lipoproteins within many organs and cell types in the human body, and it is crucial in lipid transport. It influences lipoprotein metabolism through its action as a receptor ligand that mediates the uptake of lipoprotein particles into cells, and its major function is to redistribute lipids and participate in cholesterol homeostasis (Beffert et al. 1998, Weisgraber et al. 1996). The liver is the largest producer of the protein while the brain is the second largest. In the central nervous system APOE is mainly synthesised and secreted by astrocytes and microglia, but it can also be produced in neurons (Beffert et al. 1998). It is synthesized also by macrophages and monocytes. APOE is involved in the mobilization and redistribution of cholesterol during neuronal growth and after injury, but is crucial in many other functions such as nerve regeneration, immunoregulation and also in the activation of several lipolytic enzymes (Mahley et al. 2000). The exact mechanisms by which APOE influences AD are un-

known, but the ε4 allele has been shown to intensify all the biochemical disturbances characteristics of AD, including Aβ deposition, tangle formation, neuronal cell death, oxidative stress, synaptic plasticity and dysfunctions of lipid homeostasis and cholinergic signalling (Cedazo-Minguez et al. 2001).

The first results indicating that APOE ε4 carriers have an increased risk of late-onset AD compared to the non-carriers were published in 1993 (Corder et al. 1993). Furthermore, the age at the onset of AD is known to be lower among the ε4 carriers as compared to the non-carriers (Corder et al. 1993). In contrast, the ε2 allele may be protective of AD, since it is underrepresented in persons with AD (Corder et al. 1994). However, at least one third of the persons with AD lack ε4 and as many as 50 % of people who do have ε4 survive at least to age 80 years without developing AD (Myers et al. 1996). Indeed, it has been speculated that the risk of developing AD is further modified by many other factors including several environmental and lifestyle related factors, and that the risk attributable to these factors may be further modified according to the APOE genotype. For example, the effects of smoking (Ott et al. 1998, Merchant et al. 1999, Lindsay et al. 2002, Tyas et al. 2003, Aggarwal et al. 2006, Reitz et al. 2007, Ronnemaa et al. 2011), physical activity (Rovio et al. 2005, Lindsay et al. 2002), alcohol drinking (Anttila et al. 2004, Lindsay et al. 2002), diet (Laitinen et al. 2006, Barberger-Gateau et al. 2007), and marital status (Hakansson et al. 2009) on the risk of dementia an AD have been postulated to vary according to the APOE ε4 carrier status. It seems that the ε4 allele mainly magnifies the lifestyle risks for dementia, but the results have not been consistent. It has also been suggested that the effect of the ε4 allele on the risk of AD may attenuate with increasing age in such a way that the effect diminishes after the age of 70 years (Farrer et al. 1997). However, the previous studies considering the possible modifying effect of APOE on the risk of dementia and AD have been mainly carried out among elderly cohorts with rather short follow-up times and only a few studies have investigated these gene-environmental interactions in midlife cohorts. Taken together, the long preclinical phase of AD during which the disease process evolves in the brain and the attenuating effect of APOE during aging clearly warrants further research about the gene-environmental interactions in the development of AD in various age groups and populations.

2.2.4 Smoking

The World Health Organization estimates that there are over one billion cigarette smokers in the world. Although smoking has declined in the developed countries, tobacco consumption is increasing in some developing countries. Smoking is an established risk factor for several diseases including cancer, CHD, and many pulmonary diseases, especially COPD (Bartecchi et al. 1994). However, the association of smoking with dementia and especially with AD has been controversial. Several early case-control studies suggested an inverse relation between smoking and dementia (Graves et al. 1991, Lee 1994, Van Duijn et al. 1994). Later these findings have been explained to result from selective survival; i.e. increased mortality related to smoking being even more pronounced among demented smokers (Wang et al. 1999), and consequently, long-term smokers are found out to be underrepresented among the elderly population when examining in a cross-sectional study (Riggs 1993). More recently also several prospective studies have investigated the association between smoking and dementia/AD and have yielded conflicting results. They are listed in Table 2. The first prospective study was published in 1992, and reported no association between smoking and AD in a small community-based cohort with a follow-up of 4 years (Hebert et al. 1992). There are also other studies which claim that smoking may be unrelated to dementia and AD (Yoshitake et

Table 2. The prospective studies examining the association between smoking and the risk of dementia/AD

Study	**Study population**	**Study design**	**Definition of smoking**	**Covariates**	**Outcome variable**	**Results**
Hebert et al., Boston, USA (Am J Epidemiol 1992)	Community-based cohort, N=513, 65+ years (mean age NA), F/M 55.8%/44.2%	Prospective cohort study, mean follow-up time 4.7 years	Ever and never smokers. Pack-years were also calculated.	Age, sex, education	AD	Smoking does not increase the risk of AD.
Yoshitake et al., Hisayama Study, Japan (Neurology 1995)	Community-based cohort, N=828, mean age for women 74 years and for men 73 years, F/M 59.7%/40.3%	Prospective cohort study, 7 years follow-up (mean follow-up time NA)	Smoking and non-smoking	Age	AD and VaD	Smoking does not increase the risk of AD or VaD.
Broe et al., Sydney Older Persons Study, Australia (Aust N Z J Public Health 1998)	Community-based cohort, N=327, mean age 83.4 years, F/M 49.5%/50.5%	Prospective cohort study, 3 years follow-up (mean follow-up time NA)	Current, past, never smoking	Age, sex, education	Dementia and AD	Smoking does not increase the risk of dementia or AD.
Brayne et al., Cambridge, United Kingdom (Dement Geriatr Cogn Disord 1998)	Community-based cohort, N=376, age 75+ years (mean age NA), F/M 63.6%/36.4%	Prospective cohort study, mean follow-up time 2.4 years	Current, past, never smoking	Age, sex	Dementia and AD	Smoking does not increase the risk of dementia or AD.
Ott et al., Rotterdam Study, Netherlands (Lancet 1998)	Community-based cohort, N=6870, mean age for non-smokers 71.9 years, for former smokers 68.3 years, and for current smokers 66.4 years, F/M 59.6%/40.4%	Prospective cohort study, mean follow-up time 2.1 years	Current, former, non-smokers. Pack-years (≥ 20 or < 20) were also calculated.	Age, sex, education, alcohol consumption	Dementia, AD, and VaD	Smoking increases the risk of dementia and AD among all. When analyses were stratified by the APOE ε4 carrier status, smoking increased the risk of dementia and AD only in individuals without the APOE ε4 allele. More pack-years (≥ 20) increases the risk of dementia more than fewer pack-years (< 20).

Table 2. (continued) The prospective studies examining the association between smoking and the risk of dementia/AD

Study	Study population	Study design	Definition of smoking	Covariates	Outcome variable	Results
Wang et al., Kungsholmen Project, Sweden (Am J Epidem 1999)	Population-based cohort, N=343, mean age 84.0 years, F/M for non-smokers 90%/10% and for smokers 63%/37%	Prospective cohort study, 3 years follow-up (mean follow-up time NA)	Current (defined as: current smoker; former smoker who had smoked ≥ 5 yrs or had stopped smoking after age of 40, irrespective of smoking dose; smokers who had been smoking ≥ 5 cigarettes/day if had smoked < 5 yrs or had stopped smoking before age of 40) and non-smokers	Age, sex, education	Dementia and AD	Smoking does not increase the risk of dementia or AD. (Smoking increases mortality among demented persons).
Launer et al., EURODEM network (Neurology 1999)	4 European population-based cohorts, N=12 934, 65+ years (mean age NA), F/M NA	Pooled analysis of 4 population-based prospective studies, mean follow-up time 2.2 years	Current, former, non-smokers	Age, study, sex, education	Dementia and AD	Smoking increases the risk of dementia and AD. The effect is stronger in men.
Merchant et al., Washington Heights Inwood Columbia Aging Project, USA (Neurology 1999)	Cohort of recipients of a national social insurance program Medicare, N=1062, mean age 75.1 years, F/M 68.7%/31.3%	Prospective community-based cohort study, mean follow-up time 2.0 years	Current, past, never smoking	Age, education, ethnicity	AD	Smoking increases the risk of AD. APOE ε4 slightly modifies the association: smokers without an APOE ε4 allele have the highest risk of AD compared with those with an APOE ε4 allele.
Doll et al., Cohort of British male doctors, United Kingdom (BMJ 2000)	Cohort of British male doctors, N=24 133, mean age at death 81 years	Case-control design, 47 years follow-up (mean follow-up time NA)	Current (defined as: current smokers and ex-smokers) and non-smokers	Unadjusted	Dementia, AD, VaD, Lewy body dementia	Smoking does not increase the risk of any type of dementia.
Lindsay et al., Canadian Study of Health and Aging, Canada (Am J Epidemiol 2002)	Population-based cohort, N=4088, mean age for demented 81.0 years and for non-demented 72.9 years, F/M for demented 67.5%/32.4% and for non-demented 57.5%/42.5%	Prospective cohort study, 5 years follow-up (mean follow-up time NA)	Smoking and non-smoking	Age, sex, education	AD	Smoking does not increase the risk of AD. No effect modification by the APOE ε4 carrier status.

Table 2. (continued) The prospective studies examining the association between smoking and the risk of dementia/AD

Study	Study population	Study design	Definition of smoking	Covariates	Outcome variable	Results
Tyas et al., Honolulu-Asia Aging Study, USA (Neurobiology of Aging 2004)	Community-based cohort, N=3232, 50+ years (mean age NA), Japanese American men	Prospective cohort study, data gathered over the previous 25-30 years (mean follow-up time NA)	Current, never, former smoking. Pack-years were also calculated: light (≤ 26.7), medium (> 26.7-40.5), heavy (> 40.5-55.5) and very heavy (> 55.5-156) smoking.	Age, education, APOE ε4, systolic BP, diastolic BP, use of antihypertensive medication, history of CVA, atherosclerosis, alcohol intake, FEV1	Dementia, AD, AD±CVD, and VaD	Current smokers have an increased risk of VaD, but adjustment for cardiovascular and respiratory factors mitigates the effect. Current smokers without the APOE ε4 allele have an increased risk of AD±CVD. The proportion of dementia, AD, and AD±CVD increases from light to heavy levels of smoking, but decreases at the highest level of smoking.
Moffat et al., Baltimore Longitudinal Study of Aging, USA (Neurology 2004)	Community-based cohort, N=574, mean age 66.3 years, all men	Prospective cohort study, mean follow-up time 19.1 years	Ever and never smokers	Age, BMI, diabetes, cancer, use of hormone supplements, education, testosterone level	AD	Smoking increases the risk of AD.
Juan et al., Chongqing, China (European Journal of Neurology 2004)	Community-based cohort, N=2820, mean age for non-smokers 69.2 years, for past smokers 66.9 years, and for current smokers 64.3 years, F/M NA	Prospective cohort study, 2 years follow-up (mean follow-up time NA)	Current, past (persons who had quitted for at least 6 months ago), never smoking. Pack-years were also calculated: light (≤ 26.7), medium (> 26.7-40.5), heavy (> 40.5-55.5) and very heavy (> 55.5-156) smoking.	Age, sex, education, BP, alcohol intake	Dementia, AD, AD±CVD, and VaD	Smoking increases the risk of AD, AD±CVD, and VaD. The higher level of smoking (medium and heavy) increases the risk of AD more compared to light smokers.
Luchsinger et al., New York, USA (Neurology 2005)	Cohort of recipients of a national social insurance program Medicare, N=1138, mean age 76.2 years, F/M 69.8%/30.2%	Prospective cohort study, mean follow-up time 5.5 years	Current and ever smoking	Age, gender, education, APOE, ethnic group	AD	Smoking increases the risk of AD individually, and the risk of AD increases with the number of risk factors (diabetes + hypertension + heart disease + smoking).
Aggarwal et al., Chicago Health and Aging Project, USA (Neuroepidemiology 2006)	Community-based cohort, N=1064, mean age 73.8 years F/M 61.9%/38.1%	Prospective cohort study, mean follow-up time 4.1 years	Current, former, never smoking. Pack-years were also calculated.	Time on study, age, sex, education, cognitive activities, race, APOE ε4	AD	Current smokers without the APOE ε4 allele have an increased risk of AD. Former smokers with the APOE ε4 allele have a decreased risk of AD. Former smokers also have reduced risk of AD with increasing pack-years.

Table 2. (continued) The prospective studies examining the association between smoking and the risk of dementia/AD

Study	Study population	Study design	Definition of smoking	Covariates	Outcome variable	Results
Reitz et al., Rotterdam Study, Netherlands (Neurology 2007)	Community-based cohort, N=6868, mean age 69.5 years, F/M 59.9%/40.1%	Prospective cohort study, mean follow-up time 7.1 years	Current, former, never smoking. Pack-years (≥ 20 or < 20) were also calculated.	Age, sex, education, alcohol consumption, APOE ε4	Dementia, AD, and VaD	Current smokers without the APOE ε4 allele have an increased risk of dementia and AD. More pack-years (≥ 20) increased the risk of dementia and AD more than fewer pack-years (< 20).
Peters et al., Hypertension in the Very Elderly Trial, United Kingdom (Age and Aging 2009)	Hypertensive patients recruited from 195 centres, N=3336, mean age 83.5 years, F/M 60.4%/39.6%	Randomized, double-blind, placebo-controlled multicenter trial, mean follow-up time 2 years	Current and non-smoking	Age, gender, alcohol consumption, living alone, BMI, education, piracetam use, trial medication	Dementia	Smoking does not increase the risk of dementia.
Chen et al., Anhui cohort study, China (PLoS ONE 2011)	Community-based cohort, N=1307, 65+ years (mean age NA), F/M 43.5%/56.5%	Prospective cohort study, mean follow-up time 7.5 years	Current, former, never smoking	Age, sex, BMI, urban-rurality, education, occupation, income, angina, hobbies, social network, psychosocial factors	Dementia	Smoking increases the risk of dementia.
Ronnemaa et al., Uppsala Longitudinal Study of Adult Men, Sweden (Dement Geriatr Cogn Disord 2011)	Community-based cohort, N=2268 at midlife and N=1174 at late-life, mean age 49.6 years at midlife and 71.0 years at late-life, all men	Prospective cohort study, mean follow-up 29 years (midlife) and 13 years (late-life)	Current and non-smokers	Age, education	Dementia, AD, and VaD	Midlife smoking increases the risk of dementia and VaD but not AD. At late-life the APOE ε4 non-carriers who smoke have a tendency towards an increased risk of dementia (no risk increase among the smoking APOE ε4 carriers).
Kimm et al., Korea (Archives of Gerontology and Geriatrics 2011)	Cohort of recipients of a non-profit social insurance program the National Health Insurance Corporation (NHIC), N=848505, mean age for women 53.6 years and for men 51.9 years, F/M 42.2%/57.8%	Prospective cohort study, 14 years follow-up (mean follow-up time NA)	Current (if they had smoked currently for at least 1 year), former, never smoking	Age, sex, alcohol drinking	Dementia, AD, and VaD	Smoking increases the risk of all dementia subtypes among women but not among men. Smoking is associated with dementia and AD in men < 65 years of age and in women > 65 years of age.

Abbreviations: AD=Alzheimer's disease, APOE=apolipoprotein E, BMI=body mass index, BP=blood pressure, CVA=cerebrovascular accident, CVD=cerebrovascular disease, EURODEM=European Studies of Dementia, FEV1=forced expiratory volume in 1 second, NA=not available, VaD=vascular dementia

al. 1995, Broe et al. 1998, Brayne et al. 1998, Wang et al. 1999, Doll et al. 2000, Lindsay et al. 2002, Peters et al. 2009a). On the other hand, other studies have reported that smoking does increase the risk of developing dementia, AD or VaD (Ott et al. 1998, Launer et al. 1999, Merchant et al. 1999, Tyas et al. 2003, Moffat et al. 2004, Juan et al. 2004, Luchsinger et al. 2005, Aggarwal et al. 2006, Reitz et al. 2007, Chen et al. 2011, Ronnemaa et al. 2011, Kimm et al. 2011). However, most of these studies were conducted in elderly cohorts with relatively short follow-up times (2 to 7 years). Thus far, only 3 previous studies have investigated smoking specifically in midlife in relation to late-life dementia (Tyas et al. 2003, Ronnemaa et al. 2011, Kimm et al. 2011). Findings from the Honolulu-Asia Aging Study (HAAS) indicated an increased risk of dementia, AD and VaD among midlife smokers during a follow-up time of 25 to 30 years; however, this study was conducted only among Japanese-American men (Tyas et al. 2003). The study reported also neuropathological data of 218 autopsied cases, indicating that the number of neuritic plaques increased with the amount of cigarettes smoked. Another study from Sweden, which was also conducted among men only, has reported that midlife smoking increased the risk of dementia and VaD but not AD after a follow-up of 29 years (Ronnemaa et al. 2011). Additionally, this study had another baseline at late-life (with a mean age of approximately 71 years), and in these analyses, there was no association between smoking and all types of dementia among all the participants when there was a 13 years follow-up. However, a tendency towards an increased risk of dementia was observed among the APOE ε4 non-carriers who smoke in late-life, but no risk increase was seen among the smoking APOE ε4 carriers. Yet another study with a very large cohort of 848 505 middle-aged individuals from Korea reported an increase in the risk of all dementia subtypes (dementia, AD, and VaD) among women who smoke but not among men (Kimm et al. 2011). However, when the analyses were carried out according to age group (< 65 and ≥ 65 years) smoking was found out to increase the risk of AD also in men younger than 65 years of age. With respect to women, in these analyses smoking was not found to be a significant risk factor of dementia in women aged less than 65 years, but an increased risk of AD related to smoking was observed in women of 65 years or older. There is still one small cohort study with a fairly long follow-up time of 19 years which has pointed to an increased risk of AD among ever-smokers; however, the participants were all men and since the baseline age of the participants was 66 years, it was beyond middle-age (Moffat et al. 2004).

Another limitation of the earlier studies is that the APOE ε4 carrier status of the participants has been evaluated in only a few of the studies. The studies that have taken the APOE ε4 carrier status into account indicate that this may be relevant in respect of modulating the risk of dementia among smokers. Indeed, in some of these studies, the increased risk of dementia related to smoking could be seen only among the APOE ε4 non-carriers (Ott et al. 1998, Aggarwal et al. 2006, Reitz et al. 2007, Ronnemaa et al. 2011), in one study the APOE status did not modify the risk of AD among smokers when measured by the smoking level (Tyas et al. 2003), and in one study the smoking APOE ε4 non-carriers were found out to have only a slightly more elevated risk of AD than the smoking APOE ε4 carriers (Merchant et al. 1999). Altogether, these reports suggest that the APOE ε4 non-carriers may be more prone than the APOE ε4 carriers to the deleterious effects of smoking with regard to the risk of dementia. However, previously published results from the present CAIDE study population indicate that smoking (ever vs. never) in middle age, as one of the studied lifestyle related factors (i.e. frequent alcohol drinking, physical inactivity, and high intake of saturated fatty acids and low intake of polyunsaturated fatty acids), increased the risk of dementia specifically among the APOE ε4 carriers, as compared to the non-smoking APOE ε4 non-carriers

(Kivipelto et al. 2008). Furthermore, a history of heavy smoking (≥ 1 packs per day) has been shown to lower the onset age of AD among the APOE ε4 carriers by 5 years when they were compared to non-smoking APOE ε4 non-carriers (Harwood et al. 2010). Thus, the role of APOE ε4 carrier status in modulation of dementia risk among smokers is still not clear. Nonetheless, these results suggest that the association between smoking and dementia/AD may be complex and vary according to genotype, and these connections deserve further investigation.

Only a few previous studies have considered the effect of the total accumulated smoking exposure estimated as pack-years (the average number of cigarettes daily smoked divided by 20 and multiplied by the number of years of smoking) of smoking on the risk of dementia and AD. Results from the Rotterdam Study indicated that the risk of dementia and AD was greater among persons who have smoked over 20 pack-years compared to the persons who have smoked less (Ott et al. 1998, Reitz et al. 2007). Furthermore, two studies have claimed that the risk of dementia and AD among smokers increased until the level of heavy smoking (40 to 55 pack-years), but attenuated after that, probably due to a hardy survivor effect among the very heavy smokers (55 to 156 pack-years) (Tyas et al. 2003, Juan et al. 2004). Finally, one study could detect no association between pack-years and the risk of AD among current smokers, but an inverse relationship was seen among former smokers (Aggarwal et al. 2006).

2.2.5 Pulmonary diseases

Chronic obstructive pulmonary disease (COPD) is a chronic pulmonary disease with progressive pulmonary dysfunction and in time, consequently, hypoxemia and hypercapnia. It is a major cause of death and disability worldwide (Calverley et al. 2003). There are several previous studies indicating that persons diagnosed with COPD, with (Grant et al. 1982, Incalzi et al. 1993, Ozge et al. 2006, Klein et al. 2010, Thakur et al. 2010) or without hypoxemia (Liesker et al. 2004), exhibit cognitive impairment as reflected in the deterioration of performance in various cognitive tests. However, these studies have varied markedly in terms of control groups, patient groups, test batteries and are cross-sectional in nature. Furthermore, mainly unadjusted analyses have been reported. One cross-sectional study which described results from a cohort of 1202 patients with COPD and 302 referent controls indicated that even after controlling for age, sex, race, education, and smoking, COPD was associated with more than double the risk of cognitive impairment in comparison to controls (Thakur et al. 2010). There are also some prospective studies that have examined the effect of pulmonary function on cognitive functioning and dementia. Although these studies do not address clinically diagnosed COPD but instead evaluate the effect of pulmonary function on cognitive functioning, low forced expiratory volume in 1 second (FEV1) in spirometry has become the defining feature of COPD and the basis for classification of disease severity, and thus a low FEV1 value can be a marker of COPD (Wise et al. 2006). Two early studies on elderly persons reported that baseline pulmonary function predicted cognitive change over time. The first was carried out in a cohort of 1192 community-dwelling persons aged 70 to 79 years and it revealed that lower baseline pulmonary function (as measured by peak expiratory flow (PEF) rate) predicted a greater decline in performance in cognitive tests after a 2 to 2.5 year period (Albert et al. 1995). The other study, carried out among 222 Swedish twin pairs (mean age 62 years), extended these findings by demonstrating the utility of pulmonary function (as measured by FEV1) as a predictor of cognitive performance over a 6-year longitudinal interval (Emery et al. 1998). A report from the Honolulu Heart Study was the first to assess midlife pulmonary function in relation to late-life cognitive functioning (Chyou et al. 1996). That study investigated the association between FEV1 measured in

middle age (mean age 52.5 years) and cognitive function at least 23 years later among a cohort of 3036 Japanese-American men in Hawaii. The cognitive function of the subjects was assessed by the Cognitive Abilities Screening Instrument (CASI) (Teng et al. 1994) test at late-life. Compared with men who had normal or greater than normal pulmonary function, those who had the poorest FEV1 (< 2.5 liters) at midlife had a significantly lower CASI score at late-life. Furthermore, subjects less than 55 years of age at the baseline examination showed a stronger association between baseline FEV1 and CASI than the men aged 55 or older. Subsequently, a population-based study among 1291 Swedish women with a follow-up of 20 years showed that better pulmonary functioning (as measured in PEF, FEV1 and forced vital capacity (FVC)) in midlife (mean age 52 or 58 years at baseline) was associated with a lower risk of developing dementia and AD (Guo et al. 2007). A subgroup of these women (N=379) was also studied in order to examine midlife and late-life pulmonary function in relation to small-vessel disease as assessed by brain computer tomography (CT) (Guo et al. 2006). In this study, lower midlife pulmonary function was related to white matter lesions and lacunar infarcts after a follow-up of 26 years indicative of an increased risk of small-vessel disease in late-life. The results of the Berlin Aging Study (n=437, 70+ years of age) showed that decreased pulmonary function (as indicated by impaired ventilatory capacity in spirometry) could increase the risk of clinically diagnosed dementia; however, that study was cross-sectional in nature (Schaub et al. 2000). There is still one large population-based study (N=10975) that reported an association between reduced pulmonary function (as measured in FVC and FEV1) and poorer performance in cognitive assessments at baseline and with an increased risk of dementia hospitalization during the follow-up (mean follow-up 14 years) (Pathan et al. 2011). But, no association was found between pulmonary function and cognitive decline over time. In conclusion, the focus of previous research has mainly been on the effect of COPD on various cognitive test results rather than on the actual risk of clinically diagnosed MCI or dementia. While a few studies have described an association between pulmonary function and dementia, there are no published studies that have investigated the long-term effects of diagnosed COPD on the risk of clinically diagnosed MCI and dementia in late-life.

Similarly, very little research has been conducted on long-term effects of asthma on cognitive functioning or on the risk of dementia. A Swedish study with a follow-up time of 22 years examining twin pairs did not find any association between asthma and dementia risk, although, atopy was associated with an increased risk of dementia and AD (Eriksson et al. 2008). However, a history of asthma was linked with shorter life expectancy after AD diagnosis in comparison to those individuals without an asthma history. In another cross-sectional study, asthma was not associated with dementia (Ng et al. 2007). Furthermore, one cross-sectional study revealed that subjects who had received treatment for asthma/chronic bronchitis during the last 12 months had slightly lower Mini Mental State Examination (MMSE) scores than their counterparts without these diseases (Jelicic et al. 1997). Since this issue has not been examined in detail, there is a distinct gap in our knowledge of putative associations between asthma and the long-term risk of MCI and dementia.

2.2.6 Heart diseases

Coronary heart disease (CHD) is one of the leading causes of death and disability in the world (Lopez et al. 2006). Atrial fibrillation (AF) (Go et al. 2001) and heart failure (HF) (Kannel 2000) are also common heart diseases among the elderly. These illnesses share many mutual risk factors with AD e.g. many cardiovascular risk factors are known to increase the risk of dementia and AD (Kivipelto et al. 2001, Luchsinger et al. 2005).

Table 3. The prospective studies examining the association between coronary heart disease and the risk of dementia/AD

Study	Study population	Study design	Definition of CHD	Covariates	Outcome	Results
Aronson et al., Bronx Aging Study, USA (Neurology 1990)	Community-based cohort, N=442, mean age 79.2 years, F/M 64.5%/35.5%	Prospective cohort study, 2 to 7 years follow-up (mean follow-up time NA)	MI; self-report and register data	Age, gender, Blessed IMC score, performance IQ, verbal IQ, clinical impression of diminished cognition, history of selected medical conditions, family history of dementia, diminished functional status, education, word fluency, delayed recall	Dementia	Dementia incidence is higher among women with history of MI but not among men; interaction between sex and history of MI predicted dementia "best".
Brayne et al., Cambridge, United Kingdom (Dement Geriatr Cogn Disord 1998)	Community-based cohort, N=376, age 75+ years (mean age NA), F/M 63.6%/36.4%	Prospective cohort study, mean follow-up time 2.4 years	MI; informant interview	Age, sex	Dementia and AD	History of MI increases the risk of dementia but not the risk of AD.
Ross et al., Honolulu-Asia Aging Study, USA (Neurology 1999)	Community-based cohort, N=3734, mean age 78 years, Japanese American men	Prospective cohort study, data gathered over the previous 25 years (mean follow-up time NA)	MI or AP; self-report	Age, education, western diet, hypertension, vitamin E, 1-hour postprandial glucose	VaD	CHD increases the risk of VaD. (CHD also increases the risk of stroke, and the effect is probably mediated through stroke).
Luchsinger et al., New York, USA (Neurology 2005)	Cohort of recipients of a national social insurance program Medicare, N=1138, mean age 76.2 years, F/M 69.8%/30.2%	Prospective cohort study, mean follow-up time 5.5 years	History of AF and other arrhythmias, MI, CHF, AP; self-report	Age, gender, education, APOE, ethnic group	AD	Heart disease increases the risk of AD individually, and the risk of AD increases with the number of risk factors (diabetes + hypertension + heart disease + smoking).

Table 3. (continued) The prospective studies examining the association between coronary heart disease and the risk of dementia/AD

Newman et al., Cardiovascular Health Study, USA (J Am Geriatr Soc 2005)	Community-based cohort, N=3602, median age 74 years, F/M 60%/40%	Prospective cohort study, mean follow-up time 5.4 years	MI, AP, PAD; self-report and register data, test results and medication	APOE, age, race, sex, education, MMSE, income	Dementia and AD	Any CVD increases the risk of dementia and AD (borderline significant results for MI and AP). The risk is highest in subjects with PAD. A gradient of increasing risk was noted with the extent of vascular disease.
Study	**Study population**	**Study design**	**Definition of CHD**	**Covariates**	**Outcome**	**Results**
Hayden et al., Cache County Study of Memory Health and Aging, USA (Alzheimer Dis Assoc Disord 2006)	Community-based cohort, N=3264, mean age 74.0 years, F/M 58%/42%	Prospective cohort study, mean follow-up time 3.2 years	History of MI; self-report and medication	Age, sex, education, APOE, hypertension, cholesterol, diabetes, obesity, stroke, CABG	Dementia, AD, and VaD	History of MI is not related to any form of dementia.
Chen et al., Anhui cohort study, China (PLoS ONE 2011)	Community-based cohort, N=1307, 65+ years (mean age NA), F/M 43.5%/56.5%	Prospective cohort study, mean follow-up time 7.5 years	AP; self-report	Age, sex, BMI, urban-rurality, education, occupation, income, smoking, hobbies, social network, psychosocial factors	Dementia	AP increases the risk of dementia.

Abbreviations: AD=Alzheimer's disease, AF=atrial fibrillation, AP= angina pectoris, APOE=apolipoprotein E, BMI=body mass index, CABG=coronary artery bypass graft surgery, CHD=coronary heart disease, CHF=congestive heart failure, IMC= Information-Memory-Concentration, IQ= intelligence quotient, MI=myocardial infarction, MMSE=Mini Mental State Examination, NA=not available, PAD=peripheral artery disease, VaD=vascular dementia

The discovery of AD neuropathology (amyloid plaques) in a large proportion of non-demented coronary artery disease cases at post-mortem autopsy raised a question of whether CHD could predispose to AD (Sparks et al. 1990). Later this finding was also confirmed in other studies (Soneira et al. 1996), especially among APOE ε4 carriers with CHD (Beeri et al. 2006). Atherosclerosis in cerebral vessels is also known to be associated with the occurrence of neuritic amyloid plaques in the brain, independently from cerebral infarcts (Honig et al. 2005). However, in one study there was no association detected between intracranial nor systemic atherosclerosis and AD neuropathology, although an increased risk of dementia was observed in those patients with intracranial atherosclerosis, again independently from the presence of brain infarction (Dolan et al. 2010). These interesting results can be considered as pointing to an association between CHD/atherosclerosis and dementia/AD. However, the possible association between CHD and dementia has subsequently been investigated only in a few cohort studies with elderly subjects and the results have been inconsistent. These are shown in Table 3. An early study carried out in the 1980s reported an increase in dementia incidence among women with a history of myocardial infarction (MI) (Aronson et al. 1990). Later, a small cohort study with both sexes linked a history of MI to the risk of dementia, but not to the risk of AD (Brayne et al. 1998). At the same time, a study investigating a prospective cohort of Japanese American men indicated that MI and angina pectoris (AP) would be risk factors for VaD (Ross et al. 1999). With regard to the risk of AD, early cross-sectional results from the Rotterdam study revealed that markers of generalized atherosclerosis (presence of atherosclerosis in the carotid arteries (wall thickness and plaques in ultrasonography) and of the large vessels of the legs (as assessed by the ankle-brachial index < 0.90)) existed in association not only with unspecified dementia and VaD but also with AD, and that the association was particularly clear among the APOE ε4 carriers (Hofman et al. 1997). There are also two prospective studies with a mean follow-up time of approximately 5 years which link the risk of CHD specifically to AD (Luchsinger et al. 2005, Newman et al. 2005). However, the study by Luchsinger et al. had a wide definition of heart disease including history of AF and other arrhythmias, MI, congestive heart failure (CHF) and AP, so, that study did not address CHD alone (Luchsinger et al. 2005). There has also been considerable variability in the definition of CHD in the other studies; however, almost all have viewed MI as a marker of CHD. In addition, AP and peripheral artery disease (PAD) have been regarded as markers of CHD/atherosclerosis. In fact, in the study published by Newman et al. the risk of dementia and AD was highest in individuals with PAD, however, a borderline significant increase in the risk was also observed for MI and AP (Newman et al. 2005). Finally, one recent Chinese study associated the history of AP with increased risk of dementia during a 7 year follow-up time (Chen et al. 2011). In contrast to these reports, one prospective study with a mean follow-up time of 3 years did not report any relationship between a history of MI and dementia, AD or VaD (Hayden et al. 2006). There are also studies investigating the association between CHD and cognitive functioning as assessed through different cognitive tests. CHD predisposed to later poor cognitive functioning as measured with a cognitive test battery consisting of 5 standard tests in one middle aged cohort with a median follow-up time of 11 years (Singh-Manoux et al. 2003). This seems to be the only study which would have investigated this association among a middle-aged (mean age 56 years when tested for cognitive function) cohort. There are also case-control studies which have not found any association between CHD and cognitive functioning (Grubb et al. 2000, Bursi et al. 2006). One study that addressed the role of CHD in clinically diagnosed MCI stated out that CHD was associated with MCI (Hai et al. 2011), and another study found an association to non-amnestic MCI but not to amnestic MCI (Roberts et al. 2010) in a cross-sectional setting.

AF is the most common heart rhythm disorder in elderly subjects, usually involving rapid heart rate and desynchronized electric and mechanical activity in the atria. Its prevalence increases with age and it affects up to 9 % of the population by the age of 80 (Go et al. 2001). It is a significant risk factor for cardiovascular morbidity and mortality. Already in the 1990s, cross-sectional findings from the Rotterdam Study detected a positive association between AF and dementia as well as AD with or without cerebrovascular disease (Ott et al. 1997). However, another 1990s study with a prospective cohort and a follow-up time of approximately 6 years observed no increase in the risk of all-cause or multi-infarct dementia among persons with AF (Frishman et al. 1996). It took several years before other prospective studies were published examining this issue. Table 4 shows the prospective studies investigating the association between AF and dementia/AD. The results are somewhat conflicting. One prospective cohort study, with a median follow-up time of 4.6 years, claimed that the development of dementia was common after the diagnosis of a first AF; the cumulative event rate in this study was 10.5 % at 5 years (Miyasaka et al. 2007). In addition, one large study based on over 37 000 patients on a healthcare system database stated that AF was associated with dementia, AD, and VaD after a mean follow-up of 5 years (Bunch et al. 2010). One limitation of this study was that the dementia diagnoses were based on register data. However, the cohort is the youngest of all the prospective studies examining this topic; the mean age of the participants was 60.6 years. Interestingly, the highest risk of dementia in this study cohort was observed in the younger group (< 70 years) of subjects. The mean age in the other prospective studies approached 80 years. In addition to these positive findings, there are two prospective studies, with follow-up times of 3.5 and 4 years, in which AF was not associated with dementia or AD (Rastas et al. 2007, Marengoni et al. 2011). In the Vantaa 85+ study, the mean age of the participants was as high as 88 years and the majority (80 %) were females (Rastas et al. 2007). The other study consisted of results from the Kungsholmen Project, and subjects were an average 78 years old (Marengoni et al. 2011). There is still one randomized, double-blind, placebo-controlled multicenter trial called the Hypertension in the Very Elderly Trial (HYVET), with a mean follow-up time of 2 years, which reported no association between hypertensive AF patients and dementia (Peters et al. 2009b). This study was also carried among an elderly 80+ years cohort. There are also some prospective studies which have investigated the link between AF and cognitive decline. One study did not find any association between AF and cognitive decline (Park et al. 2007), but another study observed that AF predicted a cognitive decline within the 5 year follow-up (Tilvis et al. 2004). Furthermore, AF was shown to be associated with the progression of MCI to dementia (Forti et al. 2007) and with faster AD progression (Mielke et al. 2007). There are also several works investigating this issue concentrating on patients suffering from stroke. AF is known to be a strong risk factor for stroke (Wolf et al. 1991) and stroke is known to increase the risk of dementia (Mackowiak-Cordoliani et al. 2005). Several studies have indicated that AF further increased the risk of poststroke dementia from 3 months up to 2 years after stroke (Tatemichi et al. 1990, Censori et al. 1996, Inzitari et al. 1998, Barba et al. 2000, Altieri et al. 2004, Zhou et al. 2004).

HF is a condition in which the heart cannot adequately pump enough blood to meet the body's needs. It is a frequent complication of most diseases of the heart, and its prevalence increases exponentially from the age of 60 years (Kannel 2000). There are early reports of cognitive impairment in subjects with HF primarily emerging from small case-control studies. A pooled analysis of some of these studies has indicated that CHF is associated with a pattern of generalized cognitive impairment including memory and attention deficits (Almeida

Table 4. The prospective studies examining the association between atrial fibrillation and the risk of dementia/AD

Study	Study population	Study design	Definition of AF	Covariates	Outcome	Results
Frishman et al., Bronx Longitudinal Aging Study, USA (Am Heart J 1996)	Community-based cohort, N=423, mean age 79.2 years, F/M 64%/36%	Prospective cohort study, mean follow up time 6.2 years	12-lead ECG and 24-hour ambulatory ECG	Age, gender, diabetes, hypertension, smoking, MI, stroke, LVH, BMI, cancer, drug use	All-cause and multi-infarct dementia	AF is not related to all-cause or multi-infarct dementia.
Miyasaka et al., Minnesota, USA (European Heart Journal 2007)	Community-based cohort, N=2837, mean age 71 years, F/M 47%/53%	Prospective cohort study, median follow-up time 4.6 years	First AF in ECG	Age, sex, type of AF, BMI, BP, heart rate, MI, dyslipidaemia, diabetes, smoking, peripheral or carotid artery disease, CHF, valvular heart disease, alcohol use, hyperthyroidism, renal disease, COPD, malignancy	Dementia	Development of dementia is common after the diagnosis of first AF; cumulative event rate 10.5 % at 5 years.
Rastas et al., Vantaa 85+ Study, Finland (Stroke 2007)	Population-based cohort, N=339, mean age 88.4 years, F/M 79.6%/20.4%	Prospective cohort study, mean follow-up time 3.5 years	ECG and medical records	Age, sex, hypertension, MI, CHF, diabetes, AF	Dementia	AF is not associated with dementia or AD neuropathology.
Peters et al., Hypertension in the Very Elderly Trial, United Kingdom (Journal of Hypertension 2009)	Hypertensive patients recruited from 195 centres, N=3336, age 80+ years (mean age NA), F/M 60%/40%	Randomized, double-blind, placebo-controlled multicenter trial, mean follow-up time 2 years	NA	Sex, geographical recruitment area, BMI, randomised trial treatment group, previous stroke, HF, diabetes, cholesterol, creatinine, glucose, haemoglobin	Dementia	AF is not related to the risk of dementia.
Bunch et al., Intermountain Heart Collaborative Study, USA (Heart Rhythm 2010)	Patients on the Intermountain Healthcare system database, N=37 025, mean age 60.6 years, F/M 39.9%/60.1%	Prospective observational study of consecutive patients on a non-profit healthcare system database, mean follow-up time 5 years	Medical records: ECG and diagnosis of AF	NA ("The significant and confounding factors")	Dementia, AD, VaD (register diagnoses)	AF is associated with all forms of dementia. The highest risk was in the younger group (< 70 years).
Marengoni et al., Kungsholmen Project, Sweden (Neurobiology of Aging 2011)	Community-based cohort, N=685, mean age 78 years, F/M NA	Prospective cohort study, mean follow-up time 4 years	Clinical examination, medical records, medication	Age, gender, education, hypertension, antithrombotic medication, MMSE, APOE	Dementia and AD	AF is not associated with dementia or AD.

Abbreviations: AD=Alzheimer's disease, AF=atrial fibrillation, APOE=apolipoprotein E, BMI=body mass index, BP=blood pressure, CHF=congestive heart failure, COPD=chronic obstructive pulmonary disease, ECG=electrocardiogram, HF=heart failure, LVH=left ventricular hypertrophy, MI=myocardial infarction, MMSE=Mini Mental State Examination, NA=not available, VaD=vascular dementia

et al. 2001). In addition, one prospective cohort study with a general 75+ population found an increased risk of cognitive decline during the 5 year follow-up among persons with HF (Tilvis et al. 2004). However, in the HYVET trial, HF was not related to the risk of cognitive decline among hypertensive patients (Peters et al. 2009b). The subsequent risk of dementia could not be estimated since there were too few cases with HF and dementia in the study. Thus so far only one study has examined the effect of HF on the risk of clinically diagnosed dementia in a prospective cohort study setting; it found an increased risk of both dementia and AD related to HF (Qiu et al. 2006). Furthermore, in that study, HF together with low diastolic blood pressure (< 70 mmHg) had an additive effect on the dementia risk. Another study from Italy also indicated that low systolic blood pressure (< 130 mmHg) predicted cognitive impairment among persons with HF (Zuccala et al. 2001).

3 Aims of the Study

The general aim of the study was to investigate long-term effects of midlife smoking and common pulmonary and heart diseases in midlife and late-life and the subsequent risk of dementia/AD and cognitive impairment. Special attention was paid to potential interactions between environmental and genetic risk factors. The effect of midlife smoking on the risk of later dementia was assessed in two large cohort studies with a follow-up time of over 20 years, one carried out in Finland and the other in the United States. The studies regarding pulmonary and heart diseases were performed in the Finnish cohort including data from two late-life re-examinations of the cohort after the baseline visit in midlife and subsequently during the follow-up time of over 25 years. This made it possible to assess these risk factors both in midlife and in late-life and accordingly evaluate the long-term effects of these comorbid diseases on the dementia risk at different time points. The specific aims of the present set of the studies were:

1) To study the impact of midlife smoking on the development of dementia and AD later in life taking into account also the possible modifying effect of APOE ε4 carrier status in a Finnish population (Study I).

2) To study the role of midlife smoking on the development of dementia, AD, and VaD later in life in a multiethnic American population (Study II).

3) To investigate the effect of common pulmonary diseases COPD and asthma in midlife and in late-life on the subsequent risk of cognitive impairment later in life in a Finnish population (Study III).

4) To evaluate the role of common heart diseases, i.e. atrial fibrillation, heart failure, and coronary heart disease in midlife and in late-life on the subsequent risk of dementia and AD later in life in a Finnish population (Study IV).

4 Subjects and Methods

4.1 CAIDE

Three studies (studies I, III and IV) in the present thesis are based on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study carried out in eastern Finland. CAIDE is a large, population-based study focusing on the effects of cardiovascular and lifestyle related risk factors on dementia and cognitive functioning. Participants in this study were derived from four independent, randomly selected, population-based samples originally studied within the framework of the North Karelia Project and the Finnish part of Monitoring Trend and Determinants in Cardiovascular Disease (FINMONICA) study in 1972, 1977, 1982 and 1987 (Puska et al. 1979, Puska et al. 1983, Vartiainen et al. 1994). These surveys were carried out to assess the risk factors, morbidity, and mortality attributable to cardiovascular diseases in two eastern provinces of Finland; North Karelia and Kuopio. In 1972 and 1977, a random sample of 6.6 % of the population born in 1913-1947 and living in North Karelia and Kuopio provinces was drawn. In 1982 and 1987, the sample included the age group 25-64 years and was stratified so that in both areas at least 250 subjects were chosen of each sex and in each 10-year age group. This procedure was used to comply with the international WHO MONICA project protocol (WHO MONICA Project Principal Investigators 1988). The participation rates in these baseline surveys were high, ranging from 77 % to 96 % (Vartiainen et al. 1994).

A random sample of 2000 survivors was invited to participate in the first re-examination of the CAIDE study in 1998 (Kivipelto et al. 2001). Altogether 1449 (72.5 %) individuals aged 65 to 79 years at the end of 1997, and living in two geographically defined areas in or near the towns of Kuopio and Joensuu agreed to participate. However, 40 persons who were screened at the first phase of the re-examination, and referred for further evaluation in the second phase, refused to continue in the study, leaving a total of 1409 participants with complete cognitive assessment. A second re-examination of the CAIDE study took place during 2005-2008 when all the 1426 persons of the original 2000 who were still alive and living in the geographical area were invited to participate. 909 (63.7 %) persons agreed to participate, and for 852 there is a complete cognitive assessment. During both re-examinations, the survey methods followed those applied in the midlife surveys in all respects, and additionally the cognitive status of the participants was evaluated. Figure 1 presents the formation of the CAIDE study population. The CAIDE study was approved by the Ethics Committee of Kuopio University Hospital, and the participants provided written informed consent before enrolment in the study.

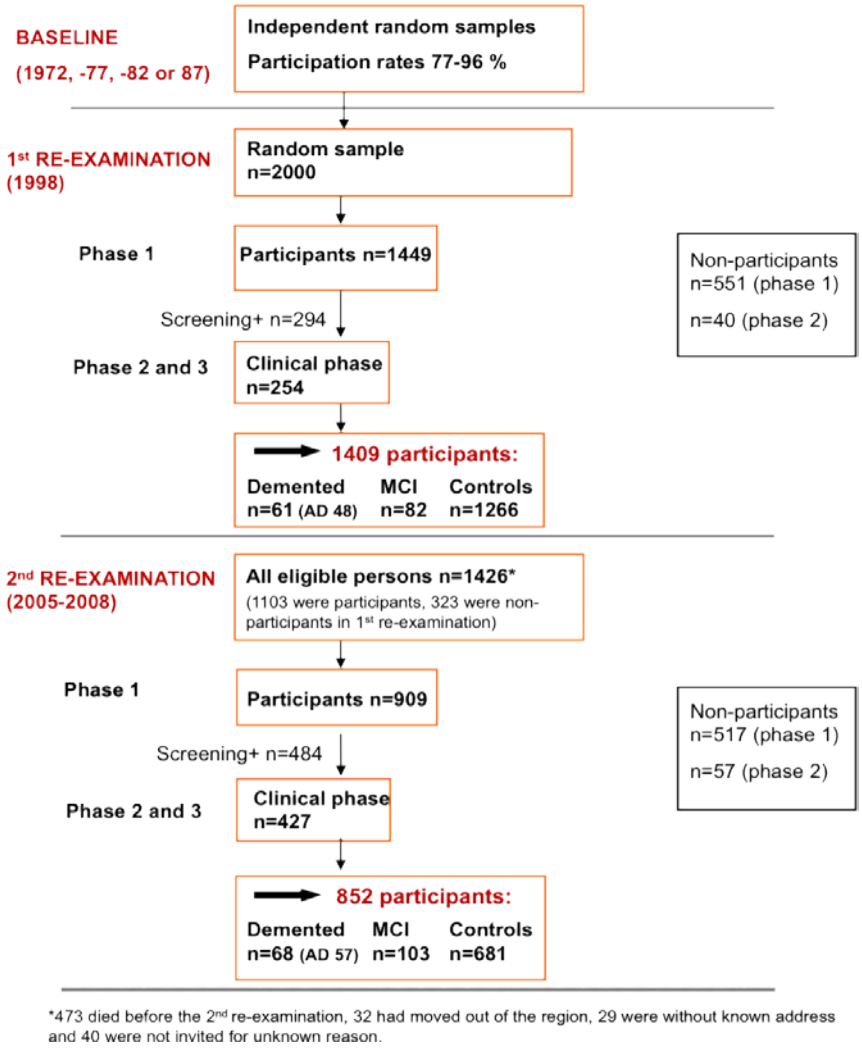

Figure 1. Formation of the CAIDE study population

4.1.1 Midlife examination

The survey methods used in the baseline (midlife) visits were carefully standardized to comply with international recommendations. They followed the WHO MONICA protocols in 1982 and 1987 (WHO MONICA Project Principal Investigators 1988), and the methods used in 1972 and 1977 were comparable with these protocols (Vartiainen et al. 1994). Briefly, the baseline surveys included a self-administered questionnaire on health behaviour, health status, and medical history of the participants. The questionnaire was sent to the participants prior to the examination, and a study nurse specifically trained for the survey checked the questionnaires during the visit to ensure that they were fully completed. Participants' systolic (SBP) and diastolic blood pressure (DBP) values were measured from the right arm after a rest period of five minutes in a seated position. Their height, and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

A venous blood sample was taken to allow determination of the serum cholesterol level. All cholesterol assays were made in the same central laboratory and the laboratory data were standardized against national and international reference laboratories.

4.1.2 First re-examination

The methods used in the first re-examination of the CAIDE study in 1998 followed those applied in the baseline surveys in all respects. Additionally the cognitive status of the participants was assessed as described later. Questions related to drug use as well as a questionnaire related to psychosocial factors were added. Furthermore, the APOE genotypes of the participants were determined from blood leukocytes by use of PCR and HhaI digestion as described by Tsukamoto and colleagues (Tsukamoto et al. 1993) with some minor modifications (Helisalmi et al. 2000). The subjects were categorized according to their APOE ε4 allele carrier status: the carriers were those with at least one APOE ε4 allele (n=499, 35.4 %) whereas the non-carriers had none (n=910, 64.6 %). The screening phase was conducted in the Department of Public Health and General Practice in the University of Kuopio and the North Karelia Project Office in Joensuu. The clinical and differential diagnostic phases were conducted in the Memory Research Clinic of the Department of Neurology of the University of Kuopio and the North Karelia Central Hospital in Joensuu

4.1.3 Second re-examination

The second re-examination of the CAIDE study was carried out during 2005-2008, and it was identical to the first re-examination with some minor modifications related to the screening criteria. All three study phases in Kuopio were conducted in the Brain Research Unit of the Clinical Research Center in the University of Kuopio. In Joensuu, the screening phase was carried out in the North Karelia Project Office and the clinical and differential diagnostic phases in the North Karelia Central Hospital.

4.1.4 Diagnostic procedure

Cognitive status of the participants was determined at both re-examinations with a three step protocol including a screening phase, a clinical phase, and a differential diagnostic phase:

1) First during the screening phase the subject and an informant were interviewed and a trained study nurse carried out a preliminary cognitive testing. These tests included:
   - Mini-Mental State Examination (MMSE) (Folstein et al. 1975) in the first re-examination and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery (Morris et al. 1989) in the second re-examination
   - Immediate word recall tests for episodic memory (Nyberg et al. 1997, Heun et al. 1998)
   - Category fluency test for semantic memory (Borkowski et al. 1967)
   - Purdue Peg Board test and letter-digit substitution test for psychomotor speed (Tiffin 1968, Wechsler 1944)
   - Stroop test for executive functioning (Stroop 1935)
   - Prospective memory task (Einstein et al. 1997)
   - Subjective memory rating (Bennett-Levy et al. 1980)

2) If the subject scored 24 or less in the MMSE, a further assessment was made in the clinical phase. Additional screening criteria used in the second re-examination to improve sensitivity to detect MCI and very mild dementia were: 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. Altogether 294 individuals fulfilled the screening criteria in the first re-examination, and 484 in the second re-examination. However, at this point some persons refused to participate in the clinical phase meaning that ultimately 254 persons (first re-examination) and 427 persons (second re-examination) proceeded to the second phase. In the clinical phase, the subjects went through a detailed physical examination carried out by a physician as well as performing a thorough neuropsychological testing conducted by a neuropsychologist. A review board consisting of the study physician and neuropsychologist, a senior neurologist and a senior neuropsychologist carefully evaluated all the available information and ascertained the preliminary diagnoses. The individuals who were judged to have possible dementia or MCI were finally invited to be the subjects of differential diagnostic examinations in the third phase of the study.

3) The differential diagnostic phase included brain computer tomography (CT)/MRI, relevant blood tests, chest radiograph, electrocardiogram, and CSF analysis if needed. All accumulated data were carefully re-evaluated by the review board before establishing the final diagnosis. Altogether 61 individuals were diagnosed with dementia, and 48 of those had AD at the first re-examination. At the second re-examination 68 subjects were diagnosed with dementia (62 were incident dementia), and 57 of those had AD (52 incident). In addition, 82 subjects received a diagnosis of MCI at the first re-examination, and 103 persons (95 were incident MCI) at the second re-examination.

4.1.5 Diagnostic criteria

The diagnosis of dementia was based on the DSM-IV criteria (American Psychiatric Association 1994) and diagnoses of probable and possible AD were based on the NINCDS-ARDRA criteria (McKhann et al. 1984). The individuals diagnosed with AD displayed generalised and/or medial temporal lobe atrophy, and none had any significant vascular pathology revealed by MRI. Isolated, minor lacunae or moderate white matter changes were not considered as exclusion criteria for AD. The AD patients scored four or less on the Hachinski Ischemia Scale (Hachinski et al. 1975). The diagnosis of VaD was based on the NINDS-AIREN criteria (Roman et al. 1993). Consensus criteria were used to diagnose other dementia types as follows: consensus diagnostic criteria for frontotemporal dementia (Neary et al. 1998), consortium for dementia with Lewy bodies (McKeith et al. 1996), and consensus criteria for alcohol related dementia (Oslin et al. 1998).

The diagnosis of MCI was made according to a modified version of the Mayo Clinic AD Research Center criteria (Smith et al. 1996, Petersen et al. 1995). These included: 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.

4.1.6 Register information

To estimate the effect of differential non-participation, information was acquired on the MCI and dementia diagnoses of the individuals from several other sources. First, dementia diagnoses of the non-participants were manually searched from medical records of local hospitals and health care centres after both re-examinations. Second, register data on medical diagnosis were available from three different national registers in Finland: the national hospital discharge register which includes information on in-patient sojourns in public hospitals (i.e. main reasons of hospitalization) starting from 1967; the Social Insurance Institution's register on the reimbursement of pharmaceutical expenses which includes information on the date when the person became entitled for reimbursement of AD drugs (donepezil, rivastigmine, galantamine, and memantine) and the dates of reimbursed drug purchases starting from 1999; and causes-of-death register where the direct and underlying causes of death are recorded. The hospital discharge diagnoses and causes of death were coded using ICD-8 - ICD-10. ICD-8 was used in Finland during 1969-1986, ICD-9 during 1987-1995, and ICD-10 from 1996 onwards.

4.2 KAISER PERMANENTE

One study (study II) of the current thesis is based on a large, multiethnic, retrospective study cohort of members of the Kaiser Permanente Medical Care Program of Northern California. Kaiser Permanente is a non-profit, integrated health maintenance organization based in Oakland, California. It was founded in 1945, and it is one of the oldest and largest health maintenance organizations in the United States. The Division of Research (DOR) was founded in 1961. DOR's research program is built on a base of rigorous epidemiologic investigation in a large, well-characterized population, and its major contributions have been in the areas of risk factor identification and prevention of diseases, including dementia. Kaiser Permanente of Northern California covers more than one fourth of the population in the geographic areas served, and the members are representative of the sociodemographics of the local population (Krieger 1992).

4.2.1 Midlife examination

The study cohort in study II comprises members of the Kaiser Permanente Medical Care Program of Northern California who participated in voluntary health examinations called the multiphasic health checkup (MHC) in San Francisco and Oakland during 1978-1985 when they were 50 to 60 years old (N=33 108). If members attended more than one MHC during this interval, data from the first visit were considered. The analytic cohort consisted of total of 21 123 people who were still alive and members of the health plan in 1994 when electronic medical record diagnoses of dementia became available. People who had missing data on the smoking questionnaire (N=1045) were excluded.

The purpose of the MHC was to collect a large amount of data on health habits and medical conditions of the subjects, and it was given as a part of routine medical care at all San Francisco and Oakland medical clinics. It included a detailed interview on health behavior, health status, medication, and medical as well as family history. Several clinical measurements were carried out: participants' height, weight, systolic and diastolic blood pressure were measured, and body mass index was calculated. In addition, a blood sample was drawn for determining serum cholesterol level. A high cholesterol level was defined as a total serum cholesterol ≥ 240 mg/dL (to convert cholesterol to millimoles per liter, multiply by 0.0259). The participants were considered to have hypertension if they had one of the following: self-report of physician

diagnosed hypertension, use of antihypertensive medication, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg. Diabetes was defined by self-report of physician diagnosed diabetes, use of insulin or oral hypoglycemic drugs, a fasting glucose (last food eaten in ≥ 8 hours) of ≥ 140 mg/dL, or a non-fasting (last food eaten in ≤ 4 hours) glucose of ≥ 200 mg/dL (to convert glucose to millimoles per liter, multiply by 0.0555). Stroke and cardiovascular disease were recorded from hospital discharge diagnoses (ICD-9 codes for ischemic stroke 433-438, hemorrhagic stroke 430-432, and for cardiovascular disease 410, 411, 413, 414, 428, 440, 443, V717) from 1978 through the end of the study. The study was approved by the Internal Review Board of Kaiser Permanente.

4.2.2 Late-life evaluation of dementia diagnoses

The dementia diagnoses of the participants were derived from an electronic medical record database which was created in 1994 and implemented in all Kaiser Permanente medical centres and clinics in 1995. The medical record form was completed by the treating physician after every outpatient or inpatient encounter. The diagnoses considered in this study included both AD (n=1136) (ICD-9-CM code 331.0) and VaD (n=416) (ICD-9-CM code 290.4) which were made by a neurologist or neuropsychologist. General dementia diagnoses (n=5367) which additionally included the diagnosis of unspecified dementia (ICD-9-CM code 290.0) were made by an internal medicine physician. The diagnoses were ascertained from January 1st, 1994 to July 31st, 2008.

4.3 STATISTICAL ANALYSES AND FORMATION OF THE STUDY POPULATION

The sociodemographic and clinical characteristics of the participants were compared using $\chi 2$ -test for categorical variables and analysis of variance or t-test for continuous variables as appropriate.

4.3.1 Study I

The first study investigated the association between midlife smoking and dementia/AD in the CAIDE population. At the time of this study, only data from the first re-examination of the CAIDE study was available.

The subjects were categorized according to their midlife smoking habits into three groups: the subjects who 1) had never smoked (=never smokers, n=826, 58.2 %), 2) had last smoked over a year ago (=former smokers, n=272, 19.2 %), and 3) had smoked within the last year (=current smokers, n=321, 22.6 %). The never smoker group was used as the reference category. Information on midlife smoking was available for 1419 (97.9 %) subjects who participated in the first re-examination. Data on smoking were missing for two demented persons (with AD) leaving the total amount of dementia and AD diagnoses in the analyses as 59 and 46, respectively.

Pack-years (the average number of cigarettes daily smoked divided by 20 and multiplied by the number of years of smoking) were also calculated to assess the subjects' long-term exposure to smoking. Pack-years could be calculated for 224 subjects (69.8 % of the current smokers), and they were dichotomized into two groups: those having smoked 1) less (n=147) or 2) more (n=77) than 20 pack-years. The first group was used as the reference category. The cut-off was based on previous studies indicating that the risk of dementia and AD might be higher after 20 pack-years of smoking (Tyas et al. 2003, Reitz et al. 2007).

Finally, it was also investigated how quitting smoking would affect the risk of developing dementia later in life. Comparable information on smoking from both midlife and the first re-examination was available for 1327 persons (91.6 %). Of them 792 reported being never smokers at both time points, 87 current smokers at both time points, and 169 persons had quit smoking between the midlife and the late-life examinations. These analyses compared the quitters to those who reported being never smokers at both time points, and also to those who were current smokers at both time points.

The impact of midlife smoking on the development of dementia/AD later in life was analyzed with logistic regression analysis resulting in odds ratios (ORs) with 95 % confidence intervals (CIs). First, the analyses were adjusted for potential sociodemographic confounders including age, sex, and education, and follow-up time (model 1). Second, also cardiovascular risk factors and events (midlife systolic blood pressure, serum cholesterol, and BMI, and late-life myocardial infarction, stroke, and diabetes/impaired glucose tolerance (diagnosed prior to the re-examination)) as well as lung diseases (asthma or/and COPD diagnosed prior to the re-examination) and the APOE carrier status of the subject (presence of at least one APOE ε4 allele) were taken into consideration (model 2). In addition, the analyses concerning the risk of both dementia and AD were repeated for the entire study sample including the data on the non-participants of the first re-examination derived from medical records (adjusted also for sociodemographic and midlife covariates). The total number of dementia cases was 117 and AD 76 in the whole study population (n=2000) when these diagnoses where taken into account.

The possible modifying effects of the APOE carrier status and sex were investigated first by stratifying the analyses separately with these factors. Second, the possible interaction between smoking and the APOE carrier status or sex was tested by adding these interaction terms separately into the fully adjusted logistic regression models. Third, combined variables were created resulting in all the possible combinations of smoking and the APOE genotype as well as smoking and sex. In these analyses, the same possible confounders as used in the main analyses were taken into consideration.

The participants with missing information for one or several covariates were excluded from the respective analyses. The statistical analyses were conducted using SPSS for Windows, release 16.0.

4.3.2 Study II

The second study was intended to cross-validate the findings from the first study in a large, multiethnic cohort of 21 123 participants with the possibility to also examine various subtypes of dementia. More specifically, this study investigated the association between smoking amount in middle age and the risk of dementia, AD, and also VaD later in life. For the analyses smoking was defined as a categorical variable with 6 levels: never smokers (n=10 205, 48.3 %), former smokers (n=6541, 31.0 %), smoking less than 0.5 pack per day (n=979, 4.6 %), 0.5-1 pack per day (n=1787, 8.5 %), 1-2 packs per day (n=1350, 6.4 %), and more than 2 packs per day (n=261, 1.2 %). The never smoker group was used as the reference category. For cases, the calculated person-years in this study included age (as time scale) in January 1st, 1994, until the age at diagnosis of dementia, AD, or VaD and, for controls, until age at death, age at date of end of Kaiser membership (as defined by a lag in health plan membership of 90 days or more), or age at end of follow-up, July 31st, 2008. Incidence rates were determined specifically for smoking categories. Age-adjusted incidence rates were calculated using the whole cohort as the standard population with 4 age groups including younger than 77 years, 77 to 81 years, 81 to 85 years, and older than 85 years.

Cox proportional hazards model (age as the time scale) resulting in hazard ratios (HRs) with 95 % CIs was used to investigate the relationship between midlife smoking and dementia, AD, and VaD. Participants were censored according to age at dementia diagnosis, age at date of death, age at lag in health plan membership, or age at the end of follow-up, July 31st, 2008. The models were first adjusted for potential sociodemographic confounders age (as time scale), sex, education (categorized as high school, trade school, college 1-2 years, college 3-4 years, and postgraduate, with grade school as a reference), race (entered as white, Asian, and other, with African American as a reference group), and marital status (classified as never married and divorced/widowed/separated, with married as a reference group). Second, the models were also adjusted for midlife BMI, hyperlipidemia, diabetes, hypertension, heart disease, and stroke (yes/no) during the follow-up. Finally, the analyses were additionally adjusted for midlife alcohol drinking (classified as former, occasionally, 1-2 drinks per day, and > 3 drinks per day, with never drinkers as a reference group). To examine whether the association between smoking and dementia, AD, or VaD was modified by sex or race, interaction terms were added to the Cox models. Because stroke is a robust predictor of dementia and also highly associated with smoking the association between smoking and dementia risk was additionally examined separately for those with and without a stroke; the final multivariate models were adjusted for both stroke during dementia follow-up (stroke from 1994 to 2008) or intercurrent stroke (stroke between baseline and the start of dementia ascertainment from 1978 to end of 1993).

Individuals with a dementia diagnosis other than the one under investigation were excluded from the analyses regarding AD or VaD separately (AD models n=17 360 and VaD models n=16 294). All analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC).

4.3.3 Study III

At the time of the third study, data on the second re-examination of the CAIDE had become available and thus were used in the study. This study examined the association between midlife and late-life self-reported COPD and asthma and the risk of cognitive impairment (MCI and dementia) in the CAIDE cohort. Information on pulmonary diseases was inquired in the self-administered questionnaire conducted at every examination visit. There were questions asking if the person had a diagnosis of pulmonary emphysema or chronic bronchitis (yes/no) (categorised in the present study as COPD) or asthma (yes/no). At the midlife examination, there were 71 subjects (4.7 %) who reported having COPD and 25 (1.7 %) had asthma. At the first re-examination, 95 individuals (7.0 %) had previously received a diagnosis of COPD and 185 (13.7 %) had been given a diagnosis of asthma. These diseases were analysed separately and also combined as one pulmonary disease variable. Accordingly, at midlife, altogether 86 (5.8 %) individuals reported having either one of these pulmonary diseases and 237 (17.5 %) persons had received the diagnosis prior to the first re-examination.

The analytic cohort of the third study comprised persons who participated in the first or second or both re-examinations (N=1511, 75.6 %). Subjects were categorised as having MCI (N=172) or dementia (N=117). Subjects with first MCI and later dementia were categorised as MCI. Since cognition is actually a continuum and MCI is regarded as a precursor of dementia, in this study MCI and dementia were ultimately combined as one outcome variable referred to as cognitive impairment (N= 289). The participants who had neither MCI nor dementia formed the control group (N=1222).

Multivariate Cox regression models were used to investigate the association between COPD, asthma, and both pulmonary diseases combined and the later risk of cognitive impairment (MCI or dementia). In the Cox regression models (follow-up time as time scale) the participants

were censored according to follow-up time at cognitive impairment diagnosis, at time of the last study visit or date of death for controls, or at end of the study (December 18th, 2008) for non-participants. First, the analyses were adjusted for sociodemographic confounders age, sex, and education (model 1). In model 2, midlife smoking status (yes/no) was added to the model. In model 3, also the APOE ε4 carrier status (yes/no), midlife self-reported physical activity (sedentary = leisure-time physical activity < 2 times/week or active = leisure-time physical activity ≥ 2 times/week), systolic blood pressure, BMI, and total serum cholesterol, and the number of late-life vascular diseases (myocardial infarction, stroke, and diabetes/impaired glucose tolerance in late-life) were included.

The analyses were carried out separately for midlife and late-life pulmonary diseases. In the analyses regarding the late-life pulmonary diseases, the individuals with midlife pulmonary diseases were excluded. In addition, for the purpose of examining incident dementia, the outcome in these analyses was considered only from the second re-examination, and those subjects who were cognitively impaired (MCI or dementia diagnose) in the first re-examination (N=143) were excluded.

To include also the non-participants in the supplementary analyses information was gathered on the MCI and dementia diagnoses of the individuals from several sources of register information as described earlier in 3.1.6. Thus finally, information on the MCI and dementia diagnoses obtained from all the available sources was combined with the diagnoses of the CAIDE study participants resulting in a total of 178 MCI and 359 dementia cases in the whole cohort (N=2000). Then the midlife analyses were repeated among the entire cohort (adjusted for the sociodemographic and midlife covariates).

Subjects with missing values for any of the variables in the respective model were also excluded from the analyses. All analyses were conducted with PASW Statistics, release 19.

4.3.4 Study IV

The fourth study examined the association between midlife and late-life heart diseases including atrial fibrillation (AF), heart failure (HF), and coronary heart disease (CHD) and the risk of dementia and AD in the CAIDE cohort. Data from both re-examinations of the CAIDE were used in the analyses. In order to obtain as accurate information as possible on the heart disease diagnoses of the subjects, information was acquired from several sources. First, information on heart diseases was inquired in the self-administered questionnaire presented at every examination visit. There were questions if the person had had a myocardial infarction (yes/no) or angina pectoris (yes/no), and if answered yes, that subject was categorised as having CHD. There was also a question about diagnosis of HF (yes/no), but information on a possible diagnosis of AF was not asked in the self-administered questionnaires. Diagnoses of CHD (ICD-8 codes: 410-414, ICD-9 codes: 410-414, and ICD-10 codes: I20-I25), AF (ICD-8 codes: 427.92, ICD-9 codes: 4273A, and ICD-10 codes: I48) and HF (ICD-8 codes: 427.00, 427.10, 782.40, ICD-9 codes: 428, 4029B, 4254A, 4148, and ICD-10 codes: I50, I50.0, I50.1, I50.9, I11.0, I13.0, I13.2) were also sought from the national hospital discharge register described above. Ultimately, all these data were combined to create the corresponding heart disease variables. Thus, the CHD and HF variables included the self-reported data as well as the register data, whereas the AF variable was based only on register data. In addition, as these heart diseases often co-exist, one combination variable was created of having at least one of these heart diseases. At midlife, altogether 98 persons had CHD, 55 had HF, 7 had AF, and 133 subjects had at least one of these diagnoses. At the first re-examination, a total of 193 persons had a diagnosis of CHD, 86 had HF, 34 had AF, and 233 participants had at least one of these diagnoses.

The analytic cohort of the fourth study is same as that investigated in the third study. However, in an attempt to refine the information on dementia diagnoses of all the individuals, these were also checked from the previously described registers. One individual was excluded from the cohort because of uncertainty of the time of the dementia diagnosis leaving a total of 1510 participants (75.5 %) in the midlife analyses. Furthermore, 8 subjects were identified as controls in the CAIDE study but had received a diagnosis of dementia based on the registries. These persons were considered as demented in these analyses. There were 127 (8.4 %) persons with dementia (of which 101 had AD) and 1383 controls in the cohort.

Flexible parametric survival models were used to investigate the association between midlife and late-life AF, HF, CHD, and all heart diseases combined and the later risk of dementia and AD. The model was chosen because it makes it possible to take into account the uncertainty of the precise timepoint when the outcome occurred. This was considered necessary due to the long follow-up times between baseline and re-examinations. Flexible parametric models for dementia-free survival time were fitted using Stata 11.2 (Stata Corp College Station, TX, USA) and stpm program. In the model, age (years) at last visit for controls, and age at first visit with dementia or age when dementia first appeared in registers (whichever came first) for cases, was considered as survival time a for all subjects. In addition, individuals who died or were lost to follow-up were censored at time a. A lower limit was also considered for survival time: assuming that the dementia diagnosed in the last visit was actually started before the last visit and after the visit before the last visit (a0). It was also assumed that individual could not be demented before the age of 60. So, max(60, a0) was considered as the lower limit for survival time, where a0 was the subject's age (years) at the visit before the last visit. Number of knots (i.e. shape of estimated spline) was selected on the basis of Akaike´s information criteria (AIC). Models with 1 to 5 knots were estimated. The model with the lowest AIC value was considered as the best fitting model. However, it was decided also to take into consideration the model parsimony: in case of almost identical AIC values the model selected was with the fewest number of knots. For some models, knot selection was not possible using evaluation AIC values (estimation was not possible due to computational problems or due to inadequate model results). In these cases it was assumed that fewer number of knots would be adequate. The choice of number of knots was also verified by plotting smoothed baseline hazard of lower and upper bound survival times and predicted hazard function against survival times and it was checked if the plot displayed evidence of more knots. The plot described above was also used to evaluate the model fit against smoothed baseline hazard of lower and upper bound survival times. If predicted hazard function was too complex compared to the smoothed baseline hazard of lower and upper bound survival times or if some of the predicted hazard values were negative, the model with the next best fit was selected on the basis of AIC and model parsimony.

All the analyses were firstly adjusted for the sociodemographic confounders sex and education in the model 1. In model 2, also midlife systolic blood pressure, total serum cholesterol level, and BMI value were added to the model. In model 3, the APOE ε4 carrier status (0 = no/1 = yes), midlife smoking status (0 = no/1 = yes) and self-reported physical activity (0 = leisure-time physical activity < 2 times/week or 1 = leisure-time physical activity ≥ 2 times/week) were included as covariates as well. The final model 4 was additionally adjusted for diabetes/impaired glucose tolerance (0 = no/1 = yes) and stroke (0 = no/1 = yes) at late-life.

The analyses were carried out separately for midlife and late-life heart diseases. In the analyses examining relationship between heart diseases at late-life (diagnosed prior to the first re-examination) and incident dementia at the second re-examination the subjects who were

already demented or non-participating in the first re-examination were excluded. In these analyses, there were 46 (6.2 %) demented participants (of which 40 had AD) and 692 controls.

There were some missing data concerning information on education, APOE status, midlife smoking and physical activity, and late-life diabetes and stroke. Since it was considered that the missing data might not be random the missing values were replaced with a mean value regarding education (mean=8.58 years) and with a value of 0.5 regarding the other categorical variables. Data on education was missing for 25 persons, APOE status for 131 persons, midlife smoking for 33 persons, midlife physical activity for 42 persons, late-life diabetes for 139 persons, and late-life stroke for 137 persons in the study cohort. The main analyses were also repeated without the imputed data, including only the subjects with no missing values in the respective analyses, to check for the effect of imputation on the results.

To explore possible interaction with the APOE ε4 allele, the analyses were stratified according to the APOE ε4 carrier status. In the analyses regarding AD as an outcome, other forms of dementia were censored at the time of the diagnosis. Finally, to evaluate the effect of non-participation, the main analyses were additionally repeated among the entire cohort including also data from the non-participants derived from the registries described in 3.1.6. (adjusted for sociodemographic and midlife vascular factors). There were a total of 408 (20.4 %) persons with dementia in these analyses.

All statistical analyses were performed with PASW Statistics, release 19 and Stata 11.2 (Stata Corp College Station, TX, USA).

5 Results

5.1 CHARACTERISTICS OF THE CAIDE STUDY POPULATION

The mean age of the participants at baseline (n=2000) was 50.6 years (SD 6.0, range 39.2 – 64.1), at the first re-examination (n=1449) 71.3 years (SD 4.0, range 65.1 – 80.4), and at the second re-examination (n=909) 78.6 years (SD 3.7, range 72.3 – 89.6). There were 900 (62.1 %) women and 549 (37.9 %) men at the first re-examination, and 590 (64.9 %) women and 319 (35.1 %) men at the second re-examination. The follow-up time of the participants at the first re-examination was on average 20.9 years (SD 4.9) and at the second re-examination 28.5 years (SD 5.0). The characteristics of the participants of the first and/or second re-examination (n=1510) and non-participants (n=490) of the study are shown in Table 5. The persons who did not participate in any re-examinations were older, had less education, had had higher values of systolic blood pressure, total serum cholesterol levels, and BMI at midlife, and were more often smokers at midlife than the participants.

Table 5. Sociodemographic and clinical characteristics of the participants and non-participants of the re-examinations

	Participants (N=1510)	**Non-participants (N=490)**	**p-value**
Age, years*			0.000
-at baseline (N=1998)	50.3 (6.0)	51.5 (5.9)	
Sex, N (%) (N=2000)			0.85
-Men	568 (37.6)	182 (37.1)	
-Women	942 (62.4)	308 (62.9)	
Education, years* (N=1953)	8.6 (3.4)	7.5 (3.1)	0.000
Midlife systolic blood pressure, mmHg* (N=2000)	144.3 (20.0)	151.2 (21.4)	0.000
Midlife total cholesterol, mmol/l* (N=2000)	6.8 (1.2)	7.0 (1.3)	0.002
Midlife body mass index, kg/m^2* (N=2000)	26.6 (3.8)	27.4 (4.4)	0.000
Midlife smoking, N (%) (N=1954)			0.004
-Yes	340 (23.0)	141 (29.6)	
Physical activity, N (%) (N=1935)			0.87
-Sedentary	874 (59.5)	280 (60.0)	
-Active	594 (40.5)	187 (40.0)	

* Values are expressed as means (SD), and t-test was used; otherwise the χ^2 test was used

5.2 SMOKING AND DEMENTIA AND ALZHEIMER'S DISEASE IN CAIDE (STUDY I)

5.2.1 Characteristics of the study population according to midlife smoking status

Sociodemographic and clinical characteristics of the study population in study I according to their midlife smoking status are shown in Table 6. Current smokers at midlife were younger and had a longer follow-up time than the former or non-smokers. Both the current and the former smokers were more often men, and had more often a history of myocardial infarction than their non-smoking counterparts. There were no differences in other sociodemographic or clinical characteristics between the midlife smoking groups. The proportion of participants with dementia (n=16, 5.0 %) and AD (n=14, 4.6 %) at the first re-examination tended to be greater

among the current smokers than among the never (dementia n=33, 4.0 %, AD n=25, 3.1 %) or former smokers (dementia n=10, 3.7 %, AD n=7, 2.6 %), but the differences between the groups did not reach statistical significance.

With respect to the non-participants (n=551) in the first re-examination, they were slightly older, less educated, and had had higher blood pressure and cholesterol levels at midlife than the participants. They were also more often current smokers at midlife (29.9 % vs. 22.6 %) and less often never-smokers (53.6 % vs. 58.2 %) or former smokers (16.4 % vs. 19.2 %). The sex distribution was similar in both groups. Furthermore, there were more demented persons (diagnoses derived from medical records) among the non-participants (8.5 %) than among the participants (4.8 %).

Table 6. Sociodemographic and clinical characteristics of the subjects in study I according to their midlife smoking status

	Never (n=826)	**Former (n=272)**	**Current (n=321)**	**P-values**
Characteristics				
Age at baseline, years*	50.7 (6.1)	51.1 (5.9)	48.8 (5.5)	p_1=0.98, p_2=0.000, p_3=0.000
Age at 1st re-examination, years*	71.4 (4.1)	71.5 (4.2)	70.8 (3.7)	p_1=1.00, p_2=0.06, p_3=0.09
Men/women, n (%)	130 (15.7)/696 (84.3)	196 (72.1)/76 (27.9)	204 (63.6)/117 (36.4)	p_1=0.000, p_2=0.000, p_3=0.03
Follow-up time, years*	20.7 (5.0)	20.4 (5.0)	22.0 (4.4)	p_1=1.00, p_2=0.000, p_3=0.000
Education, years*	8.5 (3.4)	8.9 (3.9)	8.5 (3.3)	p_1=0.42, p_2=1.00, p_3=0.61
APOE ε4 carriers/non-carriers, n (%)	276 (34.4)/526 (65.6)	97 (36.7)/167 (63.3)	120 (38.2)/194 (61.8)	p_1=0.49, p_2=0.23, p_3=0.72
Baseline				
Systolic blood pressure, mmHg*	144.5 (20.5)	145.7 (20.4)	143.6 (18.9)	p_1=1.00, p_2=1.00, p_3=0.62
Diastolic blood pressure, mmHg*	88.8 (10.8)	90.4 (11.1)	89.5 (11.5)	p_1=0.10, p_2=1.00, p_3=0.88
Total serum cholesterol, mmol/l*	6.8 (1.2)	6.7 (1.2)	6.7 (1.2)	p_1=1.00, p_2=0.63, p_3=0.98
Body mass index, kg/m²*	26.6 (3.8)	26.8 (3.5)	26.1 (3.4)	p_1=1.00, p_2=0.12, p_3=0.12
1st re-examination				
Myocardial infarction, n (%)	89 (11.0)	52 (19.3)	64 (20.3)	p_1=0.000, p_2=0.000, p_3=0.78
Stroke, n (%)	51 (6.4)	20 (7.5)	27 (8.7)	p_1=0.52, p_2=0.17, p_3=0.59
Diabetes mellitus or impaired glucose tolerance, n (%)	80 (10.0)	34 (12.8)	35 (11.2)	p_1=0.21, p_2=0.56, p_3=0.56
Lung diseases (asthma/COPD), n (%)	108 (13.7)	39 (14.9)	51 (16.4)	p_1=0.62, p_2=0.24, p_3=0.62
Dementia, n (%)	33 (4.0)	10 (3.7)	16 (5.0)	p_1=0.81, p_2=0.46, p_3=0.44
Alzheimer's disease, n (%)	25 (3.1)	7 (2.6)	14 (4.6)	p_1=0.68, p_2=0.25, p_3=0.22

*Values are expressed as means (SD), and analysis of variance was used; otherwise the χ2 test was used.
P_1 is the p-value for the differences between never and former smokers.
P_2 is the p-value for the differences between never and current smokers.
P_3 is the p-value for the differences between former and current smokers.

5.2.2 Midlife smoking and the risk of dementia and AD

Current smoking at midlife tended to increase the risk of dementia and AD later in life (at the time of the first re-examination), but the effect was not statistically significant among all participants (Table 7). When the analyses were repeated among the entire study sample also including the non-participants, the results remained statistically non-significant (for dementia OR 0.86, 95% CI 0.49-1.52 and for AD OR 1.11, 95% CI 0.56-2.20). Next it was examined whether APOE ε4 could modify the association by stratifying the analyses according to the participants' APOE carrier status. Interestingly, in these analyses, current smoking at midlife was found out to increase the risk of both dementia and AD later in life only among the APOE ε4 carriers. Among the APOE ε4 non-carriers, there was no association between smoking and the disease risk. The multiplicative interaction term between midlife smoking and the APOE carrier status was significant in the fully adjusted model (for dementia p=0.006 and for AD p=0.02). In the analyses using a combined variable with all the possible combinations of smoking and the APOE genotype, those individuals who were both APOE ε4 carriers as well as smokers had an OR of 5.33 (95% CI 1.96-14.48; Figure 2) to become demented later in life as compared to the non-smoking, non-carriers. With respect to AD, the risk increase was over 7-fold (OR 7.62, 95% CI 2.53-22.95; Figure 3). There was no effect modification found for sex in the stratified analyses, or analyses for the combined variable including smoking and sex. The interaction term between smoking and sex was also non-significant (for dementia p=0.48 and for AD p=0.45).

5.2.3 Pack-years and the risk of dementia and AD

To assess whether the amount of smoked cigarettes influences the disease risk it was decided to examine the association between pack-years of smoking at midlife and the subsequent risk of dementia/AD later in life. Pack-years could be calculated for 224 subjects (69.8 % of the current smokers). In these analyses, there was a non-significant tendency towards an increased risk of both dementia (OR 1.64, 95% CI 0.21-12.78, p=0.64) and AD (OR 1.66, 95% CI 0.21-12.94, p=0.63) with having smoked at least 20 pack-years, but the association did not reach statistical significance, probably due to compromised statistical power in these analyses.

Table 7. Midlife smoking and the risk of dementia and Alzheimer's disease

	Odds Ratio (95% Confidence Interval)		
	All participants	**APOE ε4 carrier**	**APOE ε4 non-carrier**
DEMENTIA	**n=1419, dementia 59**	**n=493, dementia 31**	**n=887, dementia 26**
Crude model			
never	1	1	1
former	0.92 (0.45-1.89)	1.87 (0.71-4.98)	0.52 (0.15-1.78)
current	1.26 (0.68-2.32)	2.93 (1.27-6.74)	0.44 (0.13-1.52)
Model 1			
never	1	1	1
former	0.65 (0.28-1.54)	1.21 (0.36-4.10)	0.42 (0.10-1.74)
current	1.20 (0.58-2.50)	3.55 (1.23-10.19)	0.40 (0.10-1.62)
Model 2			
never	1	1	1
former	0.71 (0.26-1.90)	1.58 (0.41-6.04)	0.30 (0.05-1.65)
current	1.54 (0.67-3.56)	4.93 (1.51-16.11)	0.36 (0.08-1.62)
AD	**n=1367, AD 46**	**n=477, AD 25**	**n=860, AD 21**
Crude model			
never	1	1	1
former	0.84 (0.36-1.96)	1.19 (0.36-3.88)	0.61 (0.17-2.13)
current	1.47 (0.76-2.87)	2.79 (1.15-6.76)	0.54 (0.16-1.89)
Model 1			
never	1	1	1
former	0.67 (0.25-1.81)	0.80 (0.19-3.33)	0.52 (0.12-2.31)
current	1.68 (0.75-3.78)	4.33 (1.37-13.68)	0.56 (0.13-2.38)
Model 2			
never	1	1	1
former	0.72 (0.24-2.17)	1.23 (0.27-5.54)	0.40 (0.07-2.40)
current	2.17 (0.87-5.36)	6.56 (1.80-23.94)	0.56 (0.11-2.88)

Model 1 adjusted for age, sex, education, and follow-up time
Model 2 adjusted additionally for APOE ε4 carrier status (unstratified analyses), systolic blood pressure, serum cholesterol, BMI, and history of myocardial infarction, stroke, diabetes/impaired glucose tolerance, and lung diseases

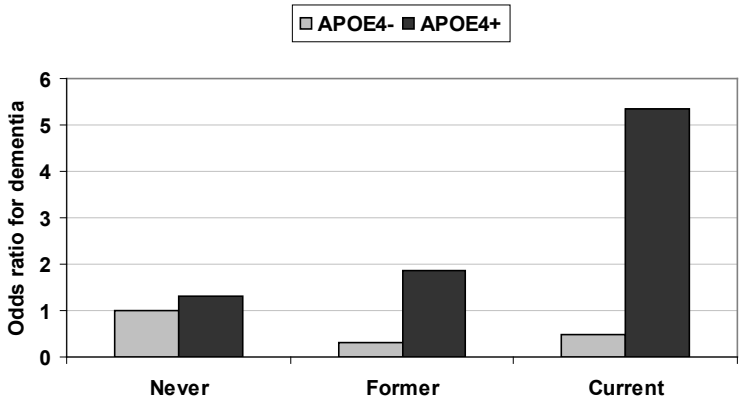

Figure 2. Combined effect of midlife smoking and the APOE ε4 carrier status on the risk of dementia later in life. Values are ORs from the logistic regression analysis adjusted for age, sex, education, follow-up time, midlife systolic blood pressure, serum cholesterol level, and BMI, and late-life myocardial infarction, stroke, diabetes/impaired glucose tolerance, and lung diseases.

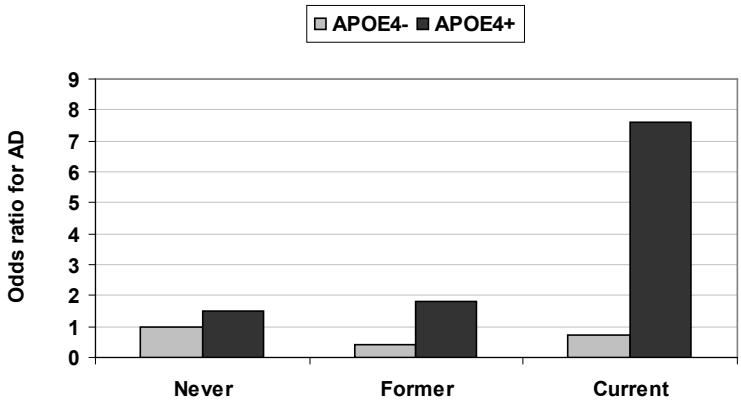

Figure 3. Combined effect of midlife smoking and the APOE ε4 carrier status on the risk of AD later in life. Values are ORs from the logistic regression analysis adjusted for age, sex, education, follow-up time, midlife systolic blood pressure, serum cholesterol level, and BMI, and late-life myocardial infarction, stroke, diabetes/impaired glucose tolerance, and lung diseases.

5.2.4 Quitting smoking and the risk of dementia and AD

The final part of this study investigated how quitting smoking after midlife would affect the risk of developing dementia/AD later in life. Among all participants, the subjects who quit smoking (n=169) between midlife and late-life examinations had a similar risk of developing dementia (OR 1.31, 95% CI 0.43-4.06, adjustments as in model 2) and AD (1.66, 95% CI 0.47-5.81) as those persons who were never smokers at both time points. However, when the analyses were stratified according to the APOE carrier status, the APOE ε4 carriers who had quit had an increased risk of dementia (4.76, 95% CI 1.01-22.47) and a tendency towards an increased risk of AD (5.40, 95% CI 0.96-30.21) compared to never smokers. There were no significant differences between the persons who quit smoking and those who were current smokers at both time points.

5.3 SMOKING AND ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA IN KAISER PERMANENTE (STUDY II)

5.3.1 Characteristics of the study population according to cognitive status

In the second study, a total of 5367 (25.4 %) persons were diagnosed with dementia (AD 1136 cases, VaD 416 cases) during a mean follow-up time of 23.1 years (SD 5.1). The mean age of the participants at baseline was 58.0 years (SD 5.4) and at the time of the dementia diagnosis, 81.5 years (SD 5.9). In all, 12 031 (57.0 %) were women and 9092 (43.0 %) were men. The sociodemographic and clinical characteristics of the study population according to cognitive status are shown in Table 8. As expected, those who were diagnosed with dementia were older, had fewer years of education and were more likely to be women than the non-demented individuals. There were differences in the occurrence of dementia between ethnic groups; compared with whites, African Americans were more likely to have a dementia diagnosis, while Asians were less likely. In addition, a higher percentage of divorced, widowed or separated persons, and a higher percentage of never drinkers were found among those with a dementia diagnosis. Dementia was also associated with a greater likelihood of having a higher mean midlife BMI value and all comorbidities.

Table 8. Sociodemographic and clinical characteristics of the participants according to cognitive status in study II

Characteristics	**Dementia n=5367**	**Non-dementia n=15 756**	**All n=21 123**	**p-value**
Age at baseline*	60.07 (5.32)	57.31 (5.28)	58.01 (5.42)	< 0.001
Age at dementia*	81.45 (5.85)	NA	81.45 (5.85)	NA
Follow-up time*	21.37 (4.27)	23.72 (5.26)	23.12 (5.13)	< 0.001
Age at 1/1/1994*	73.95 (5.51)	70.81 (5.69)	71.61 (5.81)	< 0.001
Age at censor date*	81.45 (5.85)	81.03 (6.3)	81.14 (6.2)	< 0.001
Gender, n (%)				< 0.001
Male	2131 (39.71)	6961 (44.18)	9092 (43.04)	
Race, n (%)				< 0.001
Missing	8 (0.15)	21 (0.13)	29 (0.14)	
African American	1427 (26.59)	3485 (22.12)	4912 (23.25)	
White	3411 (63.56)	9956 (63.19)	13 367 (63.28)	
Asian	321 (5.98)	1569 (9.96)	1890 (8.95)	
Other	200 (3.73)	725 (4.6)	925 (4.38)	
Education, n (%)				< 0.001
Missing	65 (1.21)	120 (0.76)	185 (0.88)	
Elementary or grade school	603 (11.24)	1413 (8.97)	2016 (9.54)	
High school	1642 (30.59)	4554 (28.9)	6196 (29.33)	
Trade/business school	520 (9.69)	1460 (9.27)	1980 (9.37)	
College 1-2 years	1130 (21.05)	3524 (22.37)	4654 (22.03)	
College 3-4 years	575 (10.71)	2017 (12.8)	2592 (12.27)	
Postgraduate	832 (15.5)	2668 (16.93)	3500 (16.57)	
Marriage, n (%)				0.002
Missing	11 (0.2)	31 (0.2)	42 (0.2)	
Married	3833 (71.42)	11 557 (73.35)	15 390 (72.86)	
Never married	218 (4.06)	718 (4.56)	936 (4.43)	
Divorced/widowed/separated	1305 (24.32)	3450 (21.9)	4755 (22.51)	
Alcohol Drinking, n (%)				< 0.001
Missing	90 (1.68)	227 (1.44)	317 (1.5)	
Never	896 (16.69)	2287 (14.52)	3183 (15.07)	
Former	197 (3.67)	633 (4.02)	830 (3.93)	
Occasionally	2778 (51.76)	8088 (51.33)	10 866 (51.44)	
1-2 drinks/day	1051 (19.58)	3235 (20.53)	4286 (20.29)	
≥ 3 drinks/day	355 (6.61)	1286 (8.16)	1641 (7.77)	
Comorbidity				
Baseline body mass index*	26.24 (4.5)	25.94 (4.4)	26.02 (4.5)	< 0.001
Baseline hypertension, n (%)	2276 (42.4)	5798 (36.8)	8074 (38.2)	< 0.001
Baseline hyperlipidemia, n (%)	3092 (57.6)	8180 (51.9)	11 272 (53.3)	< 0.001
Diabetes, n (%)	428 (7.9)	1010 (6.4)	1438 (6.8)	< 0.001
Heart Disease, n (%)	371 (6.9)	950 (6.03)	1321 (6.2)	0.02
Stroke from 1994-2008, n (%)	55 (1.0)	119 (0.7)	174 (0.8)	0.06
Stroke from 1978-1993, n (%)	293 (5.4)	522 (3.3)	815 (3.9)	< 0.001
Smoking, n (%)				< 0.001
Never	2724 (50.7)	7481 (47.4)	10 205 (48.3)	
Former	1628 (30.3)	4913 (31.1)	6541 (30.9)	
< 0.5 pack/day	234 (4.3)	745 (4.7)	979 (4.6)	
0.5-1 pack/day	435 (8.1)	1352 (8.5)	1787 (8.4)	
1-2 packs/day	283 (5.27)	1067 (6.77)	1350 (6.39)	
≥ 2 packs/day	63 (1.1)	198 (1.2)	261 (1.2)	

*Values are expressed as means (SD), and analysis of variance was used; otherwise the $\chi 2$ test was used. Abbreviations: NA=not available

5.3.2 Midlife smoking and the risk of dementia

Although both the crude incidence rates and age-adjusted incidence rates did not increase in a linear fashion according to smoking levels, there was a dramatic increase in the incidence of dementia found for those heavy smoking individuals who reported smoking more than 2 packs per day at midlife (Table 9). The calculated incidence rate of dementia in those individuals was 312.206 (95% CI 235.11-389.3) and the age-adjusted incidence rate was even higher, 786.42 (95% CI 481.23-1091.61) per 10 000 person-years. In the unadjusted Cox proportional hazards model (adjusted for age as time scale), heavy smoking at midlife doubled the later risk of dementia as compared to the situation in non-smokers. The risk increase was unchanged in the fully adjusted multivariate model; using the non-smokers as a reference group, the HR (95% CI) was 2.14 (1.65-2.78) for those smoking ≥ 2 packs per day, 1.44 (1.26-1.64) for 1-2 packs per day, and 1.37 (1.23-1.52) for 0.5-1 pack per day (Figure 4). Those who had previously smoked (HR 1.00, 95% CI 0.94-1.07) or who smoked less than 0.5 a pack per day (HR 1.04, 95% CI 0.91-1.20) in midlife had a dementia risk similar to non-smokers. An additional fully adjusted multivariate model was conducted to control only for stroke occurring between baseline and the start of the dementia assessment (intercurrent stroke), to consider the potential confounding or mediating effects of stroke which had happened prior to dementia on the smoking-dementia association. These results were not markedly different than the prior model: compared to never smokers the HR (95% CI) was 2.12 (1.64-2.75) for those smoking ≥ 2 packs per day, 1.43 (1.26-1.63) for 1-2 packs per day, and 1.36 (1.22-1.51) for 0.5-1 pack per day. Former smoking (HR 1.00, 95% CI 0.94-1.07) or smoking less than 0.5 pack per day (HR 1.05, 95% CI 0.91-1.20) was not associated with dementia risk.

5.3.3 Midlife smoking and the risk of AD

With respect to AD, the disease risk was also doubled among the midlife heavy smokers compared to those not smoking. In the fully adjusted Cox model, the association remained the same (HR 2.57, 95% CI 1.63-4.03, Figure 5). For those smoking 1-2 packs (HR 1.18, 95% CI 0.92-1.52) or 0.5-1 pack (HR 1.11, 95% CI 0.90-1.36) per day, the risk increase was borderline significant, whereas former smoking (HR 1.00, 95% CI 0.89-1.13) or smoking less than 0.5 a pack (HR 0.80, 95% CI 0.61-1.06) per day in midlife was not associated with any risk of AD later in life as compared to non-smokers.

Table 9. Age-adjusted incidence rates and crude proportional hazards of dementia, AD, and VaD risk by midlife smoking status

Smoking status	**No. of dementia cases**	**Age-adjusted incidence rate per 10 000 person-years (95% CI)**	**Dementia HR (95% CI)**	**AD HR (95% CI)**	**VaD HR (95% CI)**
Never	2724 (AD 590, VaD 210)	409.03 (392.02-426.03)	1 (reference)	1 (reference)	1 (reference)
Former	1628 (AD 351, VaD 124)	403.08 (381.05-425.11)	0.99 (0.93-1.06)	0.99 (0.89-1.11)	0.96 (0.79-1.16)
< 0.5 pack/day	234 (AD 39, VaD 17)	398.19 (337.64-458.75)	1.08 (0.94-1.23)	0.85 (0.65-1.11)	1.10 (0.73-1.66)
0.5-1 pack/day	435 (AD 89, VaD 31)	483.59 (425.64-541.54)	1.34 (1.21-1.48)	1.09 (0.89-1.33)	1.16 (0.83-1.62)
1-2 packs/day	283 (AD 50, VaD 29)	489.14 (410.44-567.85)	1.37 (1.21-1.55)	1.17 (0.92-1.48)	1.44 (1.00-2.08)
≥ 2 packs/day	63 (AD 17, VaD 5)	786.42 (481.23-1091.61)	2.01 (1.57-2.58)	2.36 (1.54-3.61)	2.02 (0.99-4.55)

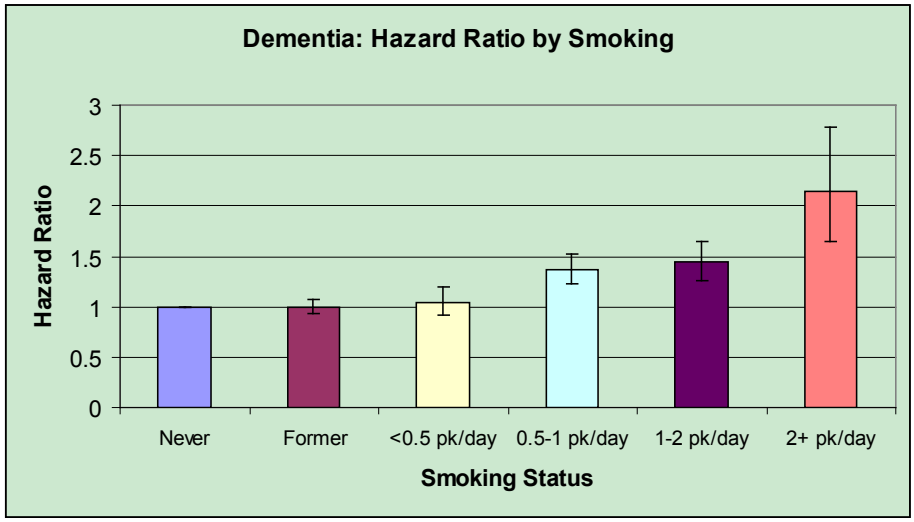

Figure 4. The risk of dementia according to midlife smoking status. Values are HRs from Cox proportional hazards model adjusted for age (as time scale), sex, education, race, marital status, hypertension, high cholesterol level, BMI, diabetes, heart disease, stroke, and alcohol drinking.

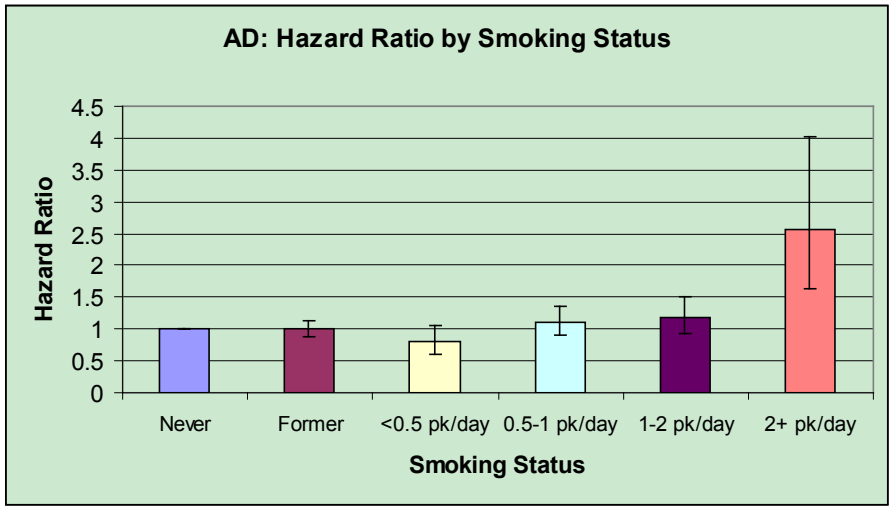

Figure 5. The risk of AD according to midlife smoking status. Values are HRs from Cox proportional hazards model adjusted for age (as time scale), sex, education, race, marital status, hypertension, high cholesterol level, BMI, diabetes, heart disease, stroke, and alcohol drinking.

5.3.4 Midlife smoking and the risk of VaD

Next it was decided to examine whether midlife smoking would also increase the risk of VaD. Despite the smaller number of VaD cases, a two-fold disease risk was also detected among the midlife heavy smokers compared to the non-smokers. Even after controlling for many potential vascular confounding factors, in the fully adjusted Cox model, those individuals smoking more than 2 packs per day at midlife were almost three times (HR 2.72, 95% CI 1.20-6.18) more

likely to develop VaD later in life than the non-smoking individuals (Figure 6). The observed risk increase was borderline significant for those smoking 1-2 packs (HR 1.42, 95% CI 0.95-2.13) per day. Former smoking (HR 0.99, 95% CI 0.80-1.22), smoking less than 0.5 a pack (HR 1.05, 95% CI 0.69-1.61), or 0.5-1 pack (HR 1.20, 95% CI 0.84-1.70) per day at midlife did not increase the later risk of VaD as compared to the non-smokers.

5.3.5 Interaction between smoking and race or sex

There were no significant interaction terms of smoking times sex or smoking times race (p values > 0.05). Post hoc stratified analyses did not reveal any trends that would have hinted at differences in the association between smoking and dementia according to race or sex.

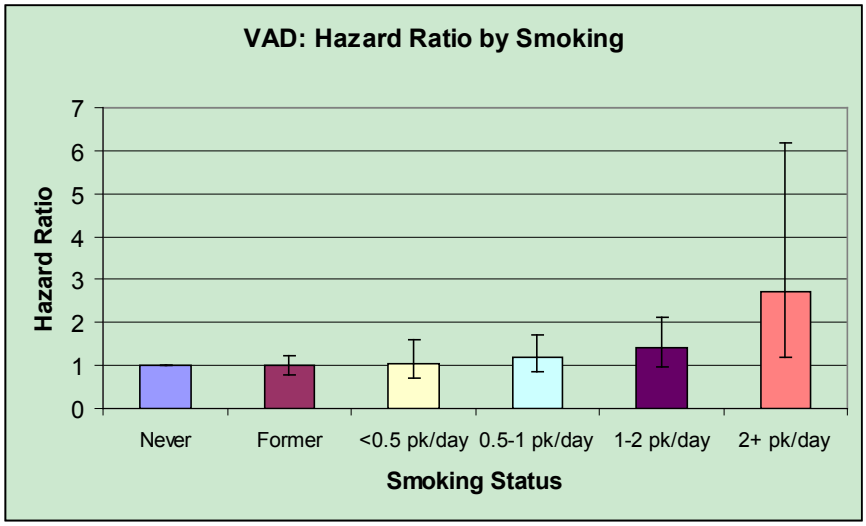

Figure 6. The risk of VaD according to midlife smoking status. Values are HRs from Cox proportional hazards model adjusted for age (as time scale), sex, education, race, marital status, hypertension, high cholesterol level, BMI, diabetes, heart disease, stroke, and alcohol drinking.

5.3.6 Sensitivity analyses by stroke status

Stroke was both highly associated with smoking (χ^2 test, $p < 0.001$) and dementia risk ($p < 0.001$), although it did not significantly interact with how smoking affected the risk of dementia, AD, or VaD ($p > 0.05$ for all interaction term models of smoking times stroke on risk). Although stroke (whether intercurrent or during follow-up) did not confound or attenuate the association between smoking and dementia risk, the association between smoking and dementia risk was examined separately for those with and without a stroke because stroke is a robust predictor of dementia and is highly associated with smoking. In these analyses, heavy smoking in midlife was shown to double the later risk for dementia, AD, and VaD even in those who had not suffered a stroke or who were without an intercurrent stroke (Table 10). However, these post-hoc subgroup analyses need to be interpreted with caution, since there were no statistically significant interaction terms of stroke times smoking on dementia risk.

Table 10. Cox proportional hazard models of smoking and dementia risk stratified by stroke status and intercurrent stroke status

	Dementia **Hazard ratio (95 % confidence interval)**		**Dementia** **Hazard ratio (95 % confidence interval)**
Among those without a stroke[a]:		**Among those without an intercurrent stroke[b]:**	
Never	1.0	Never	1.0
Former	1.01 (0.94-1.1)	Former	0.99 (0.93-1.06)
< 0.5 pack/day	0.97 (0.81-1.16)	< 0.5 pack/day	1.07 (0.94-1.23)
0.5-1 pack/day	1.38 (1.2-1.57)	0.5-1 pack/day	1.32 (1.19-1.47)
1-2 packs/day	1.44 (1.23-1.69)	1-2 packs/day	1.35 (1.19-1.54)
≥ 2 packs/day	2.19 (1.61-2.97)	≥ 2 packs/day	1.99 (1.54-2.59)
Among those with a stroke[a]:		**Among those with an intercurrent stroke[b]:**	
Never	1.0	Never	1.0
Former	0.93 (0.85-1.03)	Former	0.89 (0.68-1.17)
< 0.5 pack/day	1.29 (1.05-1.57)	< 0.5 pack/day	1.33 (0.72-2.47)
0.5-1 pack/day	1.22 (1.04-1.42)	0.5-1 pack/day	1.24 (0.85-1.82)
1-2 packs/day	1.26 (1.03-1.53)	1-2 packs/day	1.33 (0.84-2.1)
≥ 2 packs/day	1.83 (1.18-2.81)	≥ 2 packs/day	1.77 (0.72-4.37)

[a]stroke between 1994 and 2008, never smokers as a reference group
[b]stroke between 1978 and 1993, never smokers as a reference group

5.4 PULMONARY DISEASES AND COGNITIVE IMPAIRMENT IN CAIDE (STUDY III)

5.4.1 Characteristics of the study population according to cognitive status

The sociodemographic and clinical characteristics of the study population according to cognitive status are shown in Table 11.

Table 11. Sociodemographic and clinical characteristics of the participants according to cognitive status in study III

	All (N=1511)	**Control (N=1222)**	**Cognitive impairment (N=289)**	**p-value**
Follow-up time, years* (N=1511)	25.5 (6.2)	25.8 (6.2)	24.4 (5.9)	p=0.001
Age, years*				
- at baseline (N=1510)	50.3 (6.0)	50.0 (6.0)	51.5 (5.9)	p=0.000
- at 1st re-examination (N=1511)	71.2 (4.0)	70.9 (3.9)	72.2 (4.1)	p=0.000
- at 2nd re-examination (N=893)	78.6 (3.7)	78.3 (3.6)	79.5 (3.8)	p=0.000
Sex, n (%) (N=1511)				p=0.49
- Men	569 (37.7)	455 (37.2)	114 (39.4)	
- Women	942 (62.3)	767 (62.8)	175 (60.6)	
Education, years* (N=1486)	8.6 (3.4)	8.9 (3.5)	7.5 (2.8)	p=0.000
Midlife smoking, n (%) (N=1478)				p=0.47
- Yes	1138 (77.0)	927 (77.4)	211 (75.4)	
APOE ε4 carrier, n (%) (N=1380)	491 (35.6)	377 (33.5)	114 (45.1)	p=0.000
Midlife physical activity, n (%) (N=1469)				p=0.68
- Sedentary	874 (59.5)	705 (59.2)	169 (60.6)	
- Active	595 (40.5)	485 (40.8)	110 (39.4)	
Midlife systolic blood pressure, mmHg*	144.3 (20.0)	143.5 (19.4)	147.7 (22.2)	p=0.004
Midlife body mass index, kg/m²*	26.6 (3.8)	26.4 (3.8)	27.1 (3.8)	p=0.004
Midlife serum cholesterol, mmol/l*	6.8 (1.2)	6.7 (1.2)	6.9 (1.2)	p=0.02
Late-life vascular diseases, n (%) (N=1337)				p=0.017
- No	993 (74.3)	837 (76.0)	156 (66.1)	
- Yes (1 or more)	334 (25.7)	264 (24.0)	80 (33.9)	
COPD, n (%)				
- At midlife (N=1496)	71 (4.7)	53 (4.4)	18 (6.3)	p=0.16
- At 1st re-examination (N=1360)	95 (7.0)	83 (7.5)	12 (4.9)	p=0.15
Asthma, n (%)				
- At midlife (N=1493)	25 (1.7)	19 (1.6)	6 (2.1)	p=0.50
- At 1st re-examination (N=1351)	185 (13.7)	150 (13.6)	35 (14.2)	p=0.79
Pulmonary diseases combined, n (%)				
- At midlife (N=1494)	86 (5.8)	64 (5.3)	22 (7.8)	p=0.11
- At 1st re-examination (N=1351)	237 (17.5)	198 (17.9)	39 (15.9)	p=0.46

*Values are expressed as means (SD), and t-test was used; otherwise the χ^2 test was used

The individuals with cognitive impairment (MCI or dementia) were somewhat older and had a shorter follow-up time than the controls. They also had less education and were more often APOE ε4 carriers compared to the controls. The proportion of persons with midlife vascular risk factors and late-life vascular diseases was greater among the cognitively impaired subjects than among the controls. The prevalence of midlife asthma and COPD was higher and the prevalence of late-life COPD lower among the cognitively impaired individuals than among the controls, but differences between the groups were not statistically significant. There were no differences between the groups with regard to sex, midlife smoking status, or physical activity.

5.4.2 Midlife pulmonary diseases and the risk of cognitive impairment

COPD in midlife increased the later-life risk of cognitive impairment even in the fully adjusted model (model 3, HR 1.85, 95% CI 1.05 – 3.28, Table 12). The risk increase related to midlife asthma was significant in the crude model (HR 2.40, 95% CI 1.07 – 5.40), but the association became somewhat attenuated after controlling for the possible confounding factors (model 3, HR 1.88, 95% CI 0.77 – 4.63). When examining those subjects with both pulmonary diseases combined, the risk of later impaired cognition was doubled as compared with persons without these pulmonary diseases (model 3, HR 1.94, 95% CI 1.16 – 3.27).

In order to include also the non-participants the analyses were repeated in the entire study cohort (n=2000). In these analyses, the presence of midlife asthma also doubled the risk of later cognitive impairment (HR 2.09, 95% CI 1.15 – 3.80). However, adjusting for the sociodemographic and midlife covariates again attenuated the association (final model, HR 1.43, 95% CI 0.78 – 2.61). The risk increase related to midlife COPD (final model, HR 1.27, 95% CI 0.88 – 1.84) and pulmonary diseases combined (final model, HR 1.33, 95% CI 0.95 – 1.85) were almost the same, and statistically insignificant.

5.4.3 Late-life pulmonary diseases and the risk of cognitive impairment

Next the association was examined between these pulmonary diseases diagnosed in late-life, i.e. after the midlife visit but prior to the first re-examination, and incidence of cognitive impairment at the second re-examination. Interestingly, with regard to the late-life pulmonary diseases the results were opposite to those found for the midlife pulmonary diseases. Self-reported COPD (model 3, HR 0.30, 95% CI 0.08 – 1.24) or asthma (model 3, HR 0.46, 95% CI 0.18 – 1.17) in late-life tended to be inversely associated with the later risk of cognitive impairment, but the associations were not statistically significant (Table 12). However, when analysing both of these pulmonary diseases combined, it was found that they were associated with a decreased risk of subsequent cognitive impairment compared to the individuals without these diseases, even in the fully adjusted model (model 3, HR 0.42, 95% CI 0.19 – 0.93).

Table 12. Midlife and late-life pulmonary diseases (COPD, asthma and both combined) and the subsequent risk of cognitive impairment (MCI or dementia)

	Hazard Ratio (95% Confidence Interval)					
	MIDLIFE			**LATE-LIFE**		
	COPD	**Asthma**	**Both combined**	**COPD**	**Asthma**	**Both combined**
CRUDE	1.75 (1.09-2.83)	2.40 (1.07-5.40)	1.90 (1.23-2.94)	0.41 (0.13-1.29)	0.49 (0.21-1.12)	0.45 (0.22-0.92)
MODEL 1	1.44 (0.88-2.35)	1.48 (0.66-3.36)	1.57 (1.00-2.46)	0.39 (0.12-1.22)	0.49 (0.21-1.12)	0.42 (0.20-0.87)
MODEL 2	1.31 (0.78-2.21)	1.49 (0.66-3.38)	1.46 (0.91-2.34)	0.39 (0.12-1.22)	0.47 (0.20-1.08)	0.41 (0.20-0.85)
MODEL 3	1.85 (1.05-3.28)	1.88 (0.77-4.63)	1.94 (1.16-3.27)	0.30 (0.08-1.24)	0.46 (0.18-1.17)	0.42 (0.19-0.93)

Model 1 adjusted for age, sex, education
Model 2 adjusted additionally for midlife smoking
Model 3 adjusted additionally for APOE, midlife physical activity, systolic blood pressure, body mass index, and total serum cholesterol, and late-life vascular diseases

5.5 HEART DISEASES AND DEMENTIA IN CAIDE (STUDY IV)

5.5.1 Characteristics of the study population according to late-life heart disease status

Sociodemographic and clinical characteristics of the population in study IV according to late-life heart disease status are shown in Table 13. The persons with any heart disease (AF, HF, or CHD) diagnosed prior to the first re-examination were older, had less education, and a shorter follow-up time than the persons without these heart diseases. The majority of the subjects without heart diseases were female. As expected, the individuals diagnosed with these heart conditions had higher systolic blood pressure, a total serum cholesterol level, and BMI at midlife, and they also had more late-life diabetes and stroke than the healthy persons. In addition, the proportion of demented persons in both the first and the second re-examination was greater among the heart disease group than in the reference group. There were no differences between the groups according to their APOE ε4 carrier status, midlife smoking status, and physical activity.

5.5.2 Midlife heart diseases and the risk of dementia and AD

First the association was examined between heart diseases diagnosed in midlife and the subsequent risk of dementia and AD at late-life. These analyses showed (model 4) that midlife AF (HR 0.95, 95% CI 0.12 – 7.50), HF (HR 0.84, 95% CI 0.33 – 2.13), CHD (HR 0.80, 95% CI 0.38 – 1.67), or all heart diseases combined (HR 0.57, 95% CI 0.27 – 1.19) were not associated with a later risk of dementia in the unstratified analyses. The results were similar when investigating the risk of AD (model 4, for AF HR 1.11, 95% CI 0.14 – 8.65, for HF HR 1.11, 95% CI 0.43 – 2.81, for CHD HR 1.10, 95% CI 0.52 – 2.33, all heart diseases combined HR 0.78, 95% CI 0.37 – 1.63). However, when the analyses were stratified according to the APOE ε4 carrier status, the individuals who were both APOE ε4 carriers and also had a diagnosis of HF in midlife had an increased risk of both dementia (model 1, HR 2.98, 95% CI 1.05 – 8.50) and AD (model 1, HR 3.44, 95% CI 1.19 – 9.90) later in life. The association became somewhat attenuated after all adjustments for dementia (HR 2.70, 95% CI 0.90 – 8.13) but not for AD (HR 3.24, 95% CI 1.07 – 9.84). With respect to the other heart diseases or the APO ε4 non-carriers, there was no association to dementia or AD in these APOE-stratified analyses.

The main analyses were repeated of the association between midlife heart diseases and dementia among the entire cohort including also data regarding the non-participants from the registries (adjusted for sociodemographic and midlife vascular factors). These analyses produced comparable results.

Table 13. Sociodemographic and clinical characteristics of the participants according to late-life heart disease status in study IV

	All (N=1510)	**No heart diseases prior to 1st follow-up (N=997)**	**All heart diseases prior to 1st follow-up combined (N=513)**	**p-value**
Follow-up time, years* (N=1510)	25.5 (6.3)	25.9 (6.2)	24.6 (6.2)	0.000
Age, years*				
-at baseline (N=1510)	50.3 (6.0)	49.9 (6.0)	51.1 (5.9)	0.000
-at 1st re-examination (N=1414)	71.3 (4.0)	70.9 (3.9)	71.9 (4.0)	0.000
-at 2nd re-examination (N=896)	78.6 (3.7)	78.4 (3.6)	79.0 (3.8)	0.03
Sex, N (%) (N=1510)				0.000
-Men	568 (37.6)	340 (34.1)	228 (44.4)	
-Women	942 (62.4)	657 (65.9)	285 (55.6)	
Education, years* (N=1485)	8.6 (3.4)	8.9 (3.4)	8.1 (3.3)	0.000
Midlife systolic blood pressure, mmHg* (N=1510)	144.3 (20.0)	143.1 (19.2)	146.6 (21.3)	0.002
Midlife total cholesterol, mmol/l* (N=1510)	6.8 (1.2)	6.6 (1.2)	7.0 (1.2)	0.000
Midlife body mass index, kg/m²* (N=1510)	26.6 (3.8)	26.2 (3.7)	27.3 (3.8)	0.000
APOE ε4 carrier, N (%) (N=1379)	491 (35.6)	310 (35.2)	181 (36.3)	0.70
Midlife smoking, N (%) (N=1477)				0.55
-Yes	340 (23.0)	221 (22.6)	119 (23.9)	
Physical activity, N (%) (N=1468)				0.49
-Sedentary	874 (59.5)	586 (60.2)	288 (58.3)	
-Active	594 (40.5)	388 (39.8)	206 (41.7)	
Late-life diabetes, N (%) (N=1371)	147 (10.7)	55 (6.3)	92 (18.4)	0.000
Late-life stroke, N (%) (N=1373)	99 (7.2)	41 (4.7)	58 (11.7)	0.000
Dementia at 1st or 2nd re-examination, N (%) (N=1510)	127 (8.4)	72 (7.2)	55 (10.7)	0.02
Dementia at 2nd re-examination N (%), (N=738)	46 (6.2)	25 (5.0)	21 (9.0)	0.03
Alzheimer's disease at 1st or 2nd re-examination, N (%) (N=1484)	101 (6.8)	56 (5.7)	45 (8.9)	0.02
Alzheimer's disease at 2nd re-examination, N (%), (N=732)	40 (5.5)	22 (4.4)	18 (7.8)	0.06

*Values are expressed as means (SD), and t-test was used; otherwise the χ^2 test was used

5.5.3 Late-life heart diseases and the risk of dementia

Next the association between late-life heart diseases, i.e. diagnosed prior to the first re-examination, and incident dementia at the second re-examination was investigated. The results are presented in Table 14. These analyses revealed that those subjects with an AF diagnosis prior to the first re-examination had an over two-fold risk of developing dementia later in life compared to persons without AF even after all adjustments. There was also a non-significant trend towards an increased risk of subsequent dementia regarding late-life HF. CHD diagnosed prior to the first re-examination did not increase the later risk of dementia. However, the individuals with at least one of these heart diseases at late-life had an almost two-fold risk of subsequent dementia compared to those without these heart diseases.

Analyses without the imputed data including only the subjects with no missing information on the covariates produced somewhat stronger results (model 4, for AF HR 3.03, 95% CI 1.20 – 7.65, for HF HR 3.86, 95% CI 1.47 – 10.11, for CHD HR 2.24, 95% CI 1.12 – 4.49, and for all heart diseases combined HR 2.84, 95% CI 1.43 – 5.64).

Table 14. Heart diseases at late-life and the subsequent risk of dementia and AD

Hazard Ratio (95% Confidence Interval)

	Atrial fibrillation	Heart failure	Coronary heart disease	All combined
DEMENTIA				
Model 1	2.32 (0.98 – 5.52)	1.89 (0.95 – 3.75)	1.43 (0.77 – 2.66)	1.65 (0.91 – 2.97)
Model 2	2.37 (0.99 – 5.68)	1.92 (0.94 – 3.90)	1.56 (0.83 – 2.94)	1.74 (0.95 – 3.18)
Model 3	2.18 (0.89 – 5.31)	1.79 (0.87 – 3.67)	1.53 (0.81 – 2.90)	1.71 (0.93 – 3.14)
Model 4	2.61 (1.05 – 6.47)	2.06 (1.00 – 4.27)	1.66 (0.87 – 3.16)	1.94 (1.04 – 3.62)
ALZHEIMER'S DISEASE				
Model 1	2.68 (1.12 – 6.44)	1.99 (0.96 – 4.10)	1.33 (0.68 – 2.60)	1.64 (0.87 – 3.08)
Model 2	2.66 (1.10 – 6.42)	2.03 (0.96 – 4.27)	1.47 (0.74 – 2.91)	1.75 (0.92 – 3.32)
Model 3	2.53 (1.05 – 6.12)	1.84 (0.87 – 3.89)	1.39 (0.70 – 2.76)	1.68 (0.88 – 3.22)
Model 4	2.54 (1.04 – 6.16)	1.82 (0.84 – 3.97)	1.38 (0.69 – 2.77)	1.68 (0.86 – 3.26)

Model 1 adjusted for sex and education
Model 2 adjusted additionally for midlife systolic blood pressure, cholesterol, and body mass index
Model 3 adjusted additionally for APOE, midlife smoking, and physical activity
Model 4 adjusted additionally for diabetes or impaired glucose tolerance and stroke at late-life

In the analyses of the entire cohort including also the non-participants (adjusted for sociodemographic and midlife vascular factors), the association between late-life AF (HR 1.21, 95% CI 0.73 – 2.01), HF (HR 1.36, 95% CI 0.98 – 1.89), CHD (HR 1.20, 95% CI 0.91 – 1.58), and all heart diseases combined (HR 1.16, 95% CI 0.90 – 1.51) and the risk of subsequent dementia was somewhat attenuated.

5.5.4 Late-life heart diseases and the risk of AD

We also investigated late-life heart diseases in regard to subsequent risk of AD later in life. The subjects with AF prior to the first re-examination had an over two-fold risk of developing also AD at late-life compared to those without AF (Table 14). Regarding late-life HF and all heart diseases combined, there was a non-significant trend for an increased risk of AD later in life. Late-life CHD was not associated with a risk of AD.

5.5.5 Late-life heart diseases, APOE ε4 and the risk of dementia and AD

Finally it was decided to investigate whether the APOE ε4 carrier status could modify the association between late-life heart diseases and dementia risk. These APOE stratified analyses revealed that the APOE ε4 non-carriers with a AF diagnosis prior to the first re-examination had an over three-fold risk of developing subsequent dementia and six-fold risk of developing AD later in life compared to the APOE ε4 non-carriers without AF (Tables 15 and 16). The APOE ε4 non-carriers with late-life HF were also at an increased risk of AD, but the risk of dementia became attenuated after all adjustments. In the consideration of all these late-life heart diseases combined there was a trend for an increased risk of both dementia and AD later in life among the APOE ε4 non-carriers. With respect to the APOE ε4 carriers, there were no significant associations found between late-life heart diseases and the risk of developing subsequent dementia or AD.

Table 15. Heart diseases at late-life and the risk of dementia, APOE ε4 stratified analyses

Hazard Ratio (95% Confidence Interval)

	Atrial fibrillation	**Heart failure**	**Coronary heart disease**	**All combined**
APOE ε4-				
Model 1	4.19 (1.35 – 13.02)	3.17 (1.18 – 8.47)	1.65 (0.64 – 4.25)	2.93 (1.16 – 7.43)
Model 2	4.36 (1.37 – 13.84)	3.11 (1.11 – 8.72)	1.85 (0.70 – 4.90)	3.09 (1.19 – 8.01)
Model 3	4.06 (1.28 – 12.93)	2.28 (0.77 – 6.74)	1.82 (0.67 – 4.93)	2.83 (1.07 – 7.49)
Model 4	3.76 (1.15 – 12.34)	1.96 (0.62 – 6.21)	1.68 (0.61 – 4.61)	2.63 (0.94 – 7.36)
APOE ε4+				
Model 1	1.42 (0.32 – 6.25)	1.33 (0.49 – 3.59)	1.62 (0.70 – 3.75)	1.44 (0.63 – 3.28)
Model 2	1.37 (0.31 – 6.06)	1.27 (0.46 – 3.53)	1.64 (0.70 – 3.83)	1.40 (0.61 – 3.25)
Model 3	1.39 (0.31 – 6.19)	1.17 (0.41 – 3.34)	1.58 (0.67 – 3.74)	1.34 (0.57 – 3.16)
Model 4	1.42 (0.32 – 6.36)	1.24 (0.42 – 3.64)	1.68 (0.68 – 4.14)	1.40 (0.58 – 3.39)

Model 1 adjusted for sex and education
Model 2 adjusted additionally for midlife systolic blood pressure, cholesterol, and body mass index
Model 3 adjusted additionally for midlife smoking and physical activity
Model 4 adjusted additionally for diabetes or impaired glucose tolerance and stroke at late-life

Table 16. Heart diseases at late-life and the risk of AD, APOE ε4 stratified analyses

Hazard Ratio (95% Confidence Interval)

	Atrial fibrillation	**Heart failure**	**Coronary heart disease**	**All combined**
APOE ε4-				
Model 1	6.38 (1.93 – 21.04)	4.01 (1.31 – 12.27)	1.18 (0.37 – 3.82)	3.00 (1.01 – 8.84)
Model 2	6.52 (1.91 – 22.28)	4.26 (1.32 – 13.74)	1.38 (0.42 – 4.56)	3.31 (1.09 – 10.02)
Model 3	6.49 (1.87 – 22.54)	3.69 (1.09 – 12.54)	1.36 (0.40 – 4.61)	3.21 (1.04 – 9.96)
Model 4	6.05 (1.75 – 20.93)	3.69 (0.99 – 13.68)	1.20 (0.35 – 4.17)	3.01 (0.93 – 9.75)
APOE ε4+				
Model 1	1.42 (0.32 – 6.25)	1.33 (0.49 – 3.59)	1.62 (0.70 – 3.75)	1.44 (0.63 – 3.28)
Model 2	1.37 (0.31 – 6.06)	1.27 (0.46 – 3.53)	1.64 (0.70 – 3.83)	1.40 (0.61 – 3.25)
Model 3	1.39 (0.31 – 6.19)	1.17 (0.41 – 3.34)	1.58 (0.67 – 3.74)	1.34 (0.57 – 3.16)
Model 4	1.42 (0.32 – 6.36)	1.24 (0.42 – 3.64)	1.68 (0.68 – 4.14)	1.40 (0.58 – 3.39)

Model 1 adjusted for sex and education
Model 2 adjusted additionally for midlife systolic blood pressure, cholesterol, and body mass index
Model 3 adjusted additionally for midlife smoking and physical activity
Model 4 adjusted additionally for diabetes or impaired glucose tolerance and stroke at late-life

6 Discussion

6.1 SMOKING AND DEMENTIA

The current project investigated the relation between midlife smoking and the risk of late-life dementia in two separate, large, population-based studies. The first study which was carried out in a population of Finnish men and women showed that midlife smoking is associated with an increased risk of both dementia and AD after an average follow-up of 21 years; however, this effect was seen only among the APOE ε4 carriers. The second study was carried out in a large, multiethnic cohort of health plan members living in the United States and found that midlife smoking doubled the risk of dementia, as well as the subtypes AD and VaD, after 23 years follow-up; furthermore, the risk was dose dependent i.e. the risk increased with increasing amount of smoked cigarettes, and those who reported smoking more than 2 packs per day in middle age were at the greatest risk of suffering dementia in late-life.

A recent meta-analysis of 19 prospective studies, with at least 12 months of follow-up, also indicates that current smokers have almost two-fold risk of developing dementia, AD, and VaD compared to non-smoking persons (Anstey et al. 2007). On the contrary, previously several case-control studies have suggested that smoking may even be protective of dementia (Graves et al. 1991, Lee 1994, Van Duijn et al. 1994). This was speculated to be biologically plausible because of the neuroprotective effects of nicotine; the predominant component of cigarette smoke. For example, nicotine has been shown to protect neurons from excitotoxic or ischemic cell death under certain circumstances in rat cortical neurons (Shimohama et al. 1998, Akaike et al. 1994), and to be antiamyloidogenic via inhibiting Aβ formation and by breaking down already preformed Aβ (Zeng et al. 2001, Ono et al. 2002). Furthermore, nicotine may counterbalance the impairment of cholinergic neurotransmitter system present in AD by causing up-regulation of nicotinic cholinergic receptors in the brain (Benwell et al. 1988). This concept is supported by studies carried out with experimental animals as well as with AD patients which have revealed that nicotine can improve performance in cognitive tasks (Levin et al. 1998, Rusted et al. 2000). However, in addition to nicotine, cigarette smoke contains a plethora of harmful compounds (chemicals, heavy metals, free radicals), and smoking is known to predispose to many diseases including cardiovascular and cerebrovascular disease, stroke, and pulmonary diseases (especially COPD) (Bartecchi et al. 1994, Shinton et al. 1989). The association of cigarette smoking with blood vessel wall damage including endothelial injury is postulated to be an important mechanism behind the increased risk of atherosclerotic diseases related to smoking (Michael Pittilo 2000). Smoking also evokes oxidative stress and promotes inflammation in the body, thereby exacerbating mechanisms which are thought to be important in the development of AD as well (Markesbery 1997, Akiyama et al. 2000). Increased oxidative stress through several mechanisms is evident in AD, and may cause neuronal degeneration; Aβ may also contribute to this oxidative damage through the generation of free radicals. Smokers may experience more oxidative stress than non-smokers; cigarette smoke contains free radicals and it affects the inflammatory-immune systems, which then activate phagocytes that generate further oxidative damage (Traber et al. 2000). Furthermore, smokers lymphocytes are shown to exhibit more mistakes in the repair of DNA damage than cells from non-smokers, implying that smokers may have impaired cell repair mechanisms as compared to non-smokers, and consequently they may be more prone to suffer neurodegeneration (Au et al. 1991). The lower

cerebral blood flow of smokers compared to non-smokers detectable in single-photon emission computed tomography (SPECT) may also cause further neuronal damage (Siennicki-Lantz et al. 2008). Indeed, smoking is known to be associated with both reduced cortical gray matter density in brain regions associated with incipient AD (Almeida et al. 2008) and reduced microstructural integrity of cerebral white matter in MRI (Gons et al. 2011). When one considers all these negative effects of smoking on brain health, one should not be surprised that smoking would be deleterious to the brain, rather than protective against neurodegenerative diseases such as AD.

In recent years, evidence from several cohort studies has accumulated to propose that, in contrast to the results of the earlier case-control studies, smoking actually increases the risk of dementia and AD (Ott et al. 1998, Launer et al. 1999, Merchant et al. 1999, Tyas et al. 2003, Moffat et al. 2004, Juan et al. 2004, Luchsinger et al. 2005, Aggarwal et al. 2006, Reitz et al. 2007, Chen et al. 2011, Ronnemaa et al. 2011, Kimm et al. 2011). The present results are in concordance with these findings. However, there are also prospective studies which have detected no association between smoking and dementia risk (Hebert et al. 1992, Yoshitake et al. 1995, Broe et al. 1998, Brayne et al. 1998, Wang et al. 1999, Doll et al. 2000, Lindsay et al. 2002, Peters et al. 2009a). The previous case-control studies indicating an inverse relationship between smoking and dementia were probably biased by selective survival, as dementia and smoking both increase mortality and the individuals who smoke and become demented are thereby underrepresented in elderly cohorts (Riggs 1993). The more recent prospective cohort studies have also been conducted mainly in elderly cohorts with relative short follow-up times (2 to 7 years), and thus there might be some bias inherent in these studies as well, especially regarding selective survival and also possible preclinical dementia in the control subjects (Hernan et al. 2008). When investigating risk factors for a disease with a long preclinical phase, such as AD, it is essential to start the assessment before the neuropathology has significantly progressed in the brain, if one wishes to be able to investigate the factors specifically as a true long-term "risk factors", rather than a "risk predictors", for the disease. However, thus far, only three previous cohort studies have investigated the effect of smoking specifically in midlife on the risk of late-life dementia, and these have produced somewhat inconclusive results (Tyas et al. 2003, Ronnemaa et al. 2011, Kimm et al. 2011). In this respect, this present project substantially adds to the current knowledge about this matter.

The first study of the current thesis is the first in which the increased risk of dementia and AD associated with smoking was detected only among the APOE ε4 carriers whereas there was no increased risk detected among the non-carriers. There are some previous cohort studies suggesting the opposite, i.e. especially the APOE ε4 non-carriers who smoke are at an increased risk of having dementia while the smoking APOE ε4 carriers do not have an increased disease risk (Ott et al. 1998, Aggarwal et al. 2006, Reitz et al. 2007, Ronnemaa et al. 2011). In one study the APOE carrier status only slightly modified the association between smoking and dementia (Merchant et al. 1999). Furthermore, in one study which focused specifically on midlife smoking, the APOE status did not modify the relationship between pack-years of smoking and the risk of AD later in life (Tyas et al. 2003). However, the APOEε4 carrier status of the participants has been taken into account in only a few of the previous studies investigating the association between smoking and dementia; thus, since data are scarce it is difficult to draw any definite conclusions on the direction of this interaction on the disease risk. It has been speculated that those persons who are genetically susceptible to AD could benefit from smoking via stimulation of the impaired cholinergic system by the nicotine present in the cigarette smoke. However, it has also been postulated that the APOE ε4 carriers would be more vulnerable than

the non-carriers to various lifestyle related risk factors for AD (e.g. alcohol drinking, physical inactivity, and dietary fat intake), and the increase in dementia risk related to these factors is particularly high among the ε4 carriers (Kivipelto et al. 2008). Bearing in mind the harmful effects of smoking, it is really not surprising if this habit also were to increase the disease risk, in particular in already genetically susceptible persons. The mixed findings regarding the interaction between smoking and APOE on dementia risk in previous studies may be due to many factors. Firstly, it has been proposed that the effect of APOE ε4 allele on the risk of AD may attenuate with increasing age (Farrer et al. 1997). Moreover, both smoking (de Groot et al. 2004) and the APOE ε4 allele (Ewbank 2004) are known to increase mortality. Thus, the APOE ε4 carriers who survive until old age may possess some other factors protecting them not only from death, but also from dementia, and these factors may counterbalance the disease risk resulting from smoking. So, at least some effect of selective survival cannot be excluded in studies investigating this gene-environment interaction, especially in using elderly cohorts. Previous studies assessing this matter have been mainly conducted on elderly cohorts (+65 years) and the follow-up times have been relatively short (mean 2 to 7 years), with the exception of one report from the HAAS (Tyas et al. 2003). Another factor that can at least partially explain these disparate findings is the fact that in Finland and Scandinavia the proportion of APOE ε4 carriers in the population is known to be somewhat greater (in the present CAIDE study 35 %) than in some other European countries (on average 15 %) (Schiele et al. 2000). While the independent effect of the APOE ε4 allele on dementia risk (after controlling for sociodemographic and vascular factors OR 2.83, 95% CI 1.61-4.97) (Kivipelto et al. 2008) in this cohort is similar to that in other studies (Farrer et al. 1997), it is possible that also due to the higher proportion of APOE ε4 carriers examined here the effects related to this genotype are more easily detectable here than in a cohort with less APOE ε4 carriers. It would have been extremely interesting to study this interaction also in the second study of the current project with a larger, multiethnic population but, unfortunately, information on their APOE ε4 carrier status was not available.

The amount of smoking and the subsequent risk of dementia were evaluated in both current studies. In the first study the concept of pack-years was utilized. Information on pack-years could be calculated for 69.8 % of the current smokers. There was a non-significant trend towards an increased risk of both dementia and AD with having smoked at least 20 pack-years, but the association did not reach statistical significance, probably due to the compromised statistical power in these analyses. In the second study with a larger study sample, it was possible to evaluate this matter further by dividing the current smokers into categories according to the amount of cigarettes smoked in midlife. Interestingly, a dramatic increase in the incidence of dementia, AD, and VaD was found for those heavy smoking individuals who reported smoking more than 2 packs per day at midlife. Former smoking or smoking less than 0.5 a pack per day in midlife was not associated with any later dementia risk. Only a few previous studies have considered the amount of smoked cigarettes while assessing the risk of dementia attributable to smoking. The results from the second study are in concordance with the studies which indicate that heavy smoking increases the risk of dementia more than smoking fewer cigarettes (Ott et al. 1998, Tyas et al. 2003, Juan et al. 2004, Reitz et al. 2007). There is also another study in addition to the first study which did not find any association between pack-years and the risk of AD among current smokers (Aggarwal et al. 2006).

One mediating factor between smoking and dementia risk could be stroke, as smoking is a robust risk factor for stroke (Shinton et al. 1989) which in turn increases the risk of dementia, especially VaD (Mackowiak-Cordoliani et al. 2005). In the first study the analyses were adjusted for stroke but adding stroke as a covariant to the model did not attenuate the association

between smoking and dementia or AD. In the second study, heavy smoking in midlife was shown to double the later risk for dementia, AD, and VaD even among those without a stroke or without an intercurrent stroke. Thus, the association between smoking and increased risk of dementia seems to be independent from stroke.

The strengths of the first study in the current thesis are the large population-based study design, including both sexes, and the long follow-up time of the cohort. The diagnostic protocol of CAIDE study is exhaustive; consequently, the diagnoses made in the study can be considered as reliable. Moreover, due to the fact that the putative risk factors were assessed at midlife it is unlikely that subclinical dementia would have affected the subjects' smoking habits and subsequently on the results. Only in the analyses regarding quitting smoking could reverse causality or recall bias have played a role and therefore these results should be interpreted with caution. There are also some limitations regarding the first study that have to be discussed. Firstly, as the CAIDE study was undertaken in those who participated in the midlife examination and survived until the re-examination in late-life, the results can be considered as being applicable only among those middle-aged persons who survive for the next 20 years. Information about those individuals who had died prior to the first re-examination was not available at the time of this study, and therefore, the possibility of survival bias must be taken into consideration when interpreting the results. However, as previously stated, both the APOE ε4 carrier status (Ewbank 2004) and smoking (de Groot et al. 2004) have been shown to be associated with increased mortality. Accordingly, if it is assumed that among the deceased there were more APOE ε4 carriers, and that they were more likely to be demented as well, then the results would not overestimate but rather underestimate the true effects of smoking on the risk of dementia and AD later in life. Secondly, a possible bias could exist due to non-participation in the re-examination, but this is unlikely to have occurred because repeating the analyses among the whole study sample including also the non-participants did not change the results. Third, despite the relatively large cohort in the current study, the sample size was still not large enough in some of the analyses for the subgroups (especially for example the assessment of the impact of pack-years), potentially resulting in compromised statistical power and subsequently a failure to detect true associations in these analyses. One further possible limitation to be considered is the reliability of the self-reported data. However, if some misreporting regarding information about smoking habits has occurred, one would expect that it would more likely relate to the amount of smoking rather than the smoking status itself, and furthermore, occur independently of the APOE ε4 carrier status of the person; thus, ranking of individuals into different smoking categories, as conducted here, should be possible.

The second study of the present thesis is the first attempt to investigate the long-term association between smoking amount in midlife and the subsequent risk of dementia and subtypes AD and VaD later in life in a large multiethnic cohort. In this study, midlife smoking was associated with an increased risk of both AD and VaD. The relationship between smoking and VaD has not been as widely investigated as its relationship with AD. Smoking is a well established risk factor for stroke (Gorelick et al. 1999), and consequently, it can also predispose to multi-infarct dementia. Interestingly, in the current study, the association between smoking and VaD remained significant even after controlling for various potential vascular confounding factors (including stroke), thus, smoking seems to also have some independent effect on VaD, beyond its acceleration of cerebrovascular disease. It is possible that smoking can affect the development of dementia via both vascular and neurodegenerative pathways. Moreover, the availability to access to this large and diverse cohort with several ethnic groups, as well as both sexes, meant that one could investigate the interaction between smoking and race as well

as smoking and sex on the disease risk although no interactions were actually found. This is an important finding, because, despite the fact that the incidence of dementia is believed to vary by race (Gurland et al. 1999) previous studies of putative risk factors for dementia have mainly been conducted within Caucasian cohorts. The results of the second study are generalizable to elderly populations at risk for dementia. Based on these results, it is possible to postulate that the deleterious effects of smoking on dementia risk seem to be the same for both genders and across different ethnic groups.

One limitation of the second study is the definition of how dementia was diagnosed since this was obtained from medical records. Although the diagnoses were not systematically and clinically determined according to a strict study protocol, the dementia subtypes (AD and VaD) had been diagnosed by a neurologist or neuropsychologist in a memory clinic according to common clinical practice. The diagnoses of VaD in this study refer to multi-infarct dementia the diagnosis of which is more straightforward than that of AD or mixed dementia. Therefore, the diagnosis of VaD may be considered as quite reliable, while the AD group may also have included subjects with mixed dementia, as AD is more likely to be diagnosed in a person having memory impairment as a leading symptom. Furthermore, there might be some subjects with undiagnosed dementia in the cohort, and in addition, some AD and VaD cases might have been missed in the participants who died prior to the onset of the assessment in 1994. Thus, some selective survival effect cannot be ruled out with regard to the current results. Nonetheless, if one assumes that among the deceased there were more smokers, and that the deceased were also more likely to be demented, then the current results would not overestimate but rather underestimate the true effects of smoking on the risk of dementia later in life. Another limitation is that the smoking data were collected at midlife only, thus it was not possible to evaluate the effect of quitting smoking on dementia risk in this cohort. Unfortunately information on the APOE ε4 carrier status was not available for this cohort, and therefore it was not possible to ascertain the interaction between smoking and APOE ε4 carrier status on the disease risk.

6.2 PULMONARY DISEASES AND COGNITIVE IMPAIRMENT

The third study examined the association between midlife and late-life self-reported chronic obstructive pulmonary disease (COPD) and asthma and the lifelong risk of cognitive impairment (MCI and dementia) in the CAIDE population. In this study, midlife COPD and asthma were associated with an almost two-fold risk of cognitive impairment after an average of 25 years' follow-up. Adjusting for various midlife and late-life sociodemographic factors, APOE, and vascular risk factors and diseases somewhat attenuated the association between midlife asthma and cognitive impairment, but the results regarding COPD remained unchanged even after full adjustments. The results of the analyses with the combined pulmonary disease variable were also comparable; the individuals having either one of these pulmonary diseases in midlife exhibited a two-fold risk of suffering cognitive impairment later in life compared to those without these pulmonary diseases. Interestingly, pulmonary diseases diagnosed if not until later in life (between baseline visit and the first re-examination) seemed to show an inverse relationship with cognitive impairment. When analysing COPD or asthma separately, the association was not statistically significant, but when these pulmonary diseases were analysed as one combined variable they were associated with a 55 % reduced risk in the subsequent cognitive impairment compared to persons without the diseases, and the result remained the same even in the fully adjusted model.

There are several previous studies carried out during the past few decades indicating that persons diagnosed with COPD display cognitive impairment which has been measured with a variety of cognitive tests (Grant et al. 1982, Incalzi et al. 1993, Liesker et al. 2004, Ozge et al. 2006, Klein et al. 2010, Thakur et al. 2010). However, the previous studies have been mainly cross-sectional and case-control studies, and instead of the actual risk of MCI or dementia, they have focused on the effect of COPD on various cognitive test results. There are no previous prospective studies that would have examined the effect of COPD on the actual risk of developing MCI or dementia during the disease course. With regard to asthma, there is only one previous study which examined the relationship between asthma, along with some other chronic atopic disorders, and dementia after a follow-up of over 22 years (Eriksson et al. 2008). Thus, the current study is the first to examine the lifelong effect of these common pulmonary diseases on the later risk of clinically diagnosed MCI and dementia, and it fills a distinct gap in the current knowledge of putative associations between these conditions.

While interpreting current results one must consider if there is any plausible pathophysiological relation between these diseases. One would think that pulmonary diseases affect primarily the lungs, but on the other hand presumably one can speculate that they can cause cognitive impairment, i.e. dysfunction in the brain. COPD is primarily characterised by the presence of airflow limitations resulting from airway inflammation and remodelling often associated with parenchymal destruction and the development of emphysema. However, recently there has been an increasing awareness of the systemic effects of COPD. A broad array of physical functional limitations (e.g. lower extremity functioning, exercise performance, skeletal muscle strength, and self-reported limitation in basic physical actions) have been found to be specifically attributable to COPD, indicating that COPD has an impact on many body functions remote from the lung (Eisner et al. 2008). Furthermore, in many patients, the disease is associated with several systemic manifestations that can effectively result in impaired functional capacity, worsening dyspnoea, reduced health-related quality of life, and increased mortality. For example these include the presence of concomitant cardiovascular diseases, malnutrition involving primarily the loss and dysfunction of skeletal muscles, osteoporosis, anaemia, and depression. It has been proposed that increased inflammation encountered in subjects with COPD may be the link between COPD and other comorbidities and the systemic manifestations (Barnes et al. 2009). Chronic inflammation plays an important role also in the pathogenesis and expression of asthma (Chung et al. 1999). Inflammatory components are also known to be involved in the development of cognitive decline and dementia (Akiyama et al. 2000, Dziedzic 2006) and this may be one mediating factor linking these conditions. Furthermore, patients with COPD are also frequently smokers. Smoking, as well as acute exacerbations of COPD and asthma, is associated with a marked oxidant/antioxidant imbalance in the blood and thereby increased oxidative stress in the whole body, which in turn may exacerbate neurodegeneration (Rahman et al. 1996a, Rahman et al. 1996b).

There are some interesting studies which have observed a deterioration in neuropsychological tests in conjunction with altered cerebral perfusion in SPECT in persons diagnosed with COPD; hypoxemic COPD patients experience greater deteriorations in cerebral perfusion and cognitive performance compared to non-hypoxemic COPD patients or normal controls (Antonelli Incalzi et al. 2003, Ortapamuk et al. 2006). It has been postulated that the presence of a condition that lowers cerebral perfusion needs to be present before neurodegeneration and cognitive dysfunction will be expressed in AD (de la Torre 1999). Hypoperfusion ultimately leads to reduced delivery of oxygen and nutrients to the brain perhaps triggering dysfunction and death of neurons and glial cells. Moreover, one study has indicated that even mild hypox-

emia, without any impairment of the energy supply to the brain, may impair the metabolism of several crucial neurotransmitters, including acetylcholine, and in that way contribute to dysfunction in the brain (Gibson et al. 1981). According to previous research, hypoxemia seems to be a major factor in development of cognitive impairment in patients with COPD. However, cognitive dysfunction was observed also in a study which investigated non-hypoxemic, stable COPD patients (Liesker et al. 2004), and thus there are probably other contributing factors.

Asthma is associated with an increased risk of cardiovascular diseases and stroke (Iribarren et al. 2004, Onufrak et al. 2008) which are also known to increase the risk of dementia (Luchsinger et al. 2005, Newman et al. 2005, Honig et al. 2003). In addition, because of the restricted lung function related to both COPD and asthma these diseases may lead to decreased physical activity, and also sedentary lifestyle is considered as a risk factor for dementia (Rovio et al. 2005). However, in the present study, the elevated risk was detected even after controlling for physical activity, and not only for several midlife but also for late-life cardiovascular risk factors and diseases. Therefore, these factors alone do not explain the increased risk of cognitive impairment related to the pulmonary diseases in focus. Hypoxemia and hypoperfusion in the brain, increased oxidative stress, and inflammation may be some of the mechanisms leading to augmentation of neurodegeneration, and consequently, to cognitive dysfunction and dementia in patients with pulmonary diseases, although the primary disease pathology involves the lungs. However, the exact mechanisms behind the association remain to be clarified in future studies.

Interestingly, in the current study, pulmonary diseases not diagnosed until late-life (between baseline visit and the first re-examination) seemed to be associated with a lower risk of cognitive impairment later in life. There is one earlier study from Sweden which has described similar results i.e. indicating a reduction, although statistically non-significant, in the risk of AD and dementia due to asthma (Eriksson et al. 2008). However, both asthma in the elderly (Bellia et al. 2007) and restrictive pulmonary dysfunction at spirometry (possibly pointing to COPD) (Scarlata et al. 2008) are well known to increase mortality. Cognitive impairment has been shown to increase mortality as well (Stump et al. 2001). Thus, this apparently protective effect in the late-life analyses may be due to poorer survival among the cognitively impaired persons with pulmonary diseases thereby reflecting selective survival rather than a true protective effect of pulmonary diseases against cognitive impairment. This concept is also supported by findings from the Swedish study which indicate that individuals with a history of asthma have a shorter life expectancy after AD diagnosis than subjects without asthma (Eriksson et al. 2008). Another possible explanation for the present findings may be that as the pathophysiological processes leading to cognitive impairment and dementia require decades to develop, pulmonary diseases not diagnosed until in late-life may not have sufficient time to affect the risk of cognitive decline and dementia. One could argue that advances in both diagnoses and medical treatment of pulmonary disorders may also have resulted in the fact that the pulmonary diseases reported at the time of the midlife examination were more severe than those reported at the time of the late-life examination. Moreover, subjects who are diagnosed with pulmonary diseases only later in life may have some other factors (i.e. more effective cell repair mechanisms) protecting them from pulmonary disease earlier; these same factors may protect these individuals from progressing to dementia and may counterbalance the increased disease risk resulting from pulmonary diseases.

The strengths of the third study include the thorough study protocol of the CAIDE study, which increases the reliability of the results. One possibility for the some survival bias exists also regarding the third study; however, if some survival bias did exist it would probably un-

derestimate the association between pulmonary diseases and cognitive impairment and dementia, not the opposite. There might also be some bias considering the self-reported data. In particular, the COPD diagnoses in this study may also include some other chronic pulmonary diseases, probably mostly asthma. Especially among the elderly population, the distinction between asthma and COPD may be difficult, and individuals may also have components of both diseases (i.e. both obstructive and restrictive pulmonary dysfunction features). Therefore, analyses with the variable including both pulmonary diseases combined were also carried out but they produced comparable results. However, some bias due to misclassification may have occurred regarding the categorization to asthma and COPD.

6.3 HEART DISEASES AND DEMENTIA AND ALZHEIMER'S DISEASE

The fourth study aimed to assess the role of three common heart diseases atrial fibrillation (AF), heart failure (HF), and coronary heart disease (CHD) diagnosed in midlife and in late-life on the later risk of subsequent dementia and AD in the CAIDE population after an average follow-up of 25 years. In this study, AF diagnosed in late-life (prior to the first re-examination) was an independent risk factor for later dementia and AD; the risk was more than doubled compared to persons without AF in late-life. Late-life HF tended to increase the risks as well. CHD alone at late-life was not associated with subsequent dementia or AD later in life. However, the presence of at least one of these heart diseases prior to the first re-examination increased the late-life risk of dementia; the subsequent increased risk of AD was borderline significant. The associations were somewhat modified by the APOE ε4 carrier status; in the stratified analyses, the increased risk of dementia and AD related to late-life heart diseases was seen only among the APOE ε4 non-carriers. The diagnosis of AF or CHD already in midlife did not have any effect on the risk of dementia later in life, but the APOE ε4 carriers with HF in middle age had an increased risk of both dementia and AD later in life. In summary, these results indicate that these common heart diseases, especially AF, in late-life may predispose the individual also to subsequent dementia. Our results also suggest that the effect of genetic predisposition may affect the disease risk differently at different time points in life, a matter which has not been previously investigated with regard to heart diseases.

Earlier cohort studies which have investigated the association between AF and dementia have given mixed results. Some studies have indicated an increased risk of dementia (Frishman et al. 1996, Rastas et al. 2007, Peters et al. 2009b, Marengoni et al. 2011). However, these studies have been carried out among elderly cohorts (mean age approximately 60 to 80 years) and the follow-up times have been short (2 to 6 years). Regarding CHD (Aronson et al. 1990, Brayne et al. 1998, Ross et al. 1999, Luchsinger et al. 2005, Newman et al. 2005, Hayden et al. 2006, Chen et al. 2011) and HF (Qiu et al. 2006) only few previous cohort studies with elderly subjects and inconsistent results have investigated the possible association between these diseases and the risk of dementia. Thus, our study is the first one to investigate these associations in a cohort with a baseline assessment in midlife and a long follow-up time of approximately 25 years. Furthermore, we were able to examine heart diseases at different time points in life, thus obtaining a more comprehensive picture of the lifelong effect of these heart diseases on the subsequent dementia risk.

The mechanisms behind the association between heart diseases and dementia are still unclear. There is clear evidence for the role of vascular factors in VaD (Erkinjuntti et al. 2009). This seems plausible since VaD is related to stroke and small vessel disease which are undoubtedly related to vascular risk factors. Subjects with AF are at a risk of suffering a stroke by throm-

boembolism which can further predispose to dementia (Lip et al. 2007). AF is known to alter hemostatic function by increasing both thrombin generation and fibrin turnover in subjects with AF and dementia compared with those without dementia, and long-term use of warfarin, an anticoagulant drug, has been postulated to be protective against dementia in patients with AF (Barber et al. 2004). Recent data also indicate that HF is associated with an altered hemostasis, namely a prothrombotic state, which can lead to thromboembolic stroke (Davis et al. 2000). However, the increased risk of both dementia and AD related to late-life AF was seen even after adjusting for stroke, i.e. there probably are also some other underlying mechanisms involved in the association. It is not currently fully understood how vascular factors contribute to the pathogenesis of AD, which is neuropathologically characterized by the deposition of amyloid plaques and neurofibrillary tangles in the brain. Interestingly, in animal studies using a cholesterol-fed rabbit model of human CHD, both the production and accumulation of intraneuronal β-amyloid in the brain was detected in the cholesterol-fed rabbits (Sparks et al. 2000). One could argue that the link between heart diseases and AD could be at least partially mediated through cholesterol, as hypercholesterolemia predisposes both to AD and CHD. However, the results from clinical studies investigating the role of lipid lowering medication statins in reducing the risk of AD have not been consistent (Pac-Soo et al. 2011). In the present study, the risk increase related to late-life heart diseases was not changed when including cholesterol into the analyses suggesting that other mechanisms might be behind the association. Patients with heart diseases often take very limited physical activity and adopt a sedentary lifestyle both of which are considered as risk factors for dementia (Rovio et al. 2005). However, in our study the increased risk of dementia and AD was observed even after controlling for midlife physical activity, as well as for several other midlife and late-life cardiovascular risk factors and diseases; therefore, these factors alone do not explain the increased risk of dementia and AD related to heart diseases found here.

There are also other common factors between CHD and AD. The major genetic risk factor for AD, the APOE ε4 allele, also increases the risk of CHD (Davignon et al. 1988). The vulnerability to CHD may be mediated through the increased risk of hypercholesterolemia in APOE ε4 carriers. Furthermore, there is evidence to suggest that APOE E4 protein has less antioxidant effects than APOE E3 protein (Casserly et al. 2004). As both atherosclerosis and AD are associated with increased oxidative stress which is known to contribute to the disease pathogenesis, any loss of protective antioxidant factors may exacerbate this kind of damage (Markesbery 1997). In addition to oxidative stress, the APOE ε4 allele has been shown to intensify all the biochemical disturbances which are characteristic of AD, i.e. Aβ deposition, tangle formation, neuronal cell death, synaptic plasticity, and dysfunctions of lipid homeostasis and cholinergic signaling (Cedazo-Minguez et al. 2001). One further common factor in CHD and AD is the increased level of inflammation in the body (Akiyama et al. 2000, Hansson 2005). Inflammation plays a key role in CHD and in other manifestations of atherosclerosis (Hansson 2005). Inflammation has also been shown to have a direct role in the initiation, maintenance, and recurrence of AF although the underlying mechanisms are unknown (Issac et al. 2007). When accumulated over many years, direct and bystander damage from increased inflammation in the body may exacerbate the pathogenic processes related to AD (Akiyama et al. 2000).

Still one further interesting putative mechanism mediating the relation between heart diseases and dementia may be associated with the decreased cardiac output which is present in several heart diseases, following cerebral hypoperfusion and subsequent neuronal damage (de la Torre 2006). In AF, the unsynchronized atrial and ventricular contraction can lead to impaired pump function and subsequently to diminished blood flow from the heart to systemic

circulation inducing a significant brain hypoperfusion (Gomez et al. 1992). Brain hypoperfusion can be present also in HF, i.e. a condition in which the heart cannot adequately pump enough blood to meet the body's needs (Alves et al. 2005). HF is actually often the end stage of CHD and hypertensive heart disease (Kannel 2000), which are also the most common underlying disorders in AF (Krahn et al. 1995). According to one theory, the reduction in the cerebral blood flow due to heart diseases may trigger the development of AD pathology in the brain in individuals whose cerebral perfusion is already threatened by advanced age (de la Torre 2006). Furthermore, chronic brain hypoperfusion may result in a neuronal energy crisis leading in defects in protein synthesis that later result in AD neurodegenerative lesions such as the formation of β-amyloid plaques and neurofibrillary tangles. In one report from the Rotterdam Study, low cerebral blood flow was shown to be associated with dementia and also with markers of incipient dementia, suggesting that cerebral hypoperfusion precedes and possibly contributes to onset of clinical dementia (Ruitenberg et al. 2005). Ultimately, there are several separate factors that can affect the neurodegenerative process through various direct and indirect pathways and can act in synergistic manner, and in time, result in clinical dementia.

Curiously, AF or CHD diagnosed already in midlife did not have any effect on the later dementia risk in the current study. These findings are of special interest, because one might expect that the longer a condition predisposing to a disease has time to affect, then greater would be the risk. One factor influencing the present findings may be that the number of heart disease diagnoses emerging in midlife was quite small. On the other hand, the long follow-up time between baseline and the diagnosis of dementia may have permitted more effective treatment of hypertension and other cardiovascular risk factors along with beneficial changes in lifestyle during the follow-up years in subjects with midlife heart diseases, resulting in lowered dementia risk. Furthermore, in one large observational study, the increased risk of death among demented persons with AF was greatest in the less elderly persons (< 70 years) and became non-significant in the older groups (> 80 years) (Bunch et al. 2010). Consequently, this lack of association may be due to poorer survival of those demented patients with heart diseases, thereby reflecting selective survival.

We observed that APOE ε4 carriers suffering HF at midlife had an increased risk of dementia and AD. APOE ε4 carriers are known to be more vulnerable to the deleterious effects of various risk factors for AD (e.g. alcohol drinking, physical inactivity, and dietary fat intake) (Kivipelto et al. 2008). However, when the late-life analyses were stratified by the APOE ε4 carrier status, a statistically significant increase in dementia risk related to heart diseases was observed only among the APOE ε4 non-carriers. This may be due to several factors. First, it has been suggested that the effect of APOE ε4 allele on the risk of AD may be attenuated with increasing age (Farrer et al. 1997). Thus those subjects with the APOE ε4 allele who survive disease free until old age may have some other factors (i.e. more effective cell repair mechanisms) which protect them from falling ill. Furthermore, because APOE ε4 allele increases the risk of CHD as well as the risk of dementia, the lack of association among the APOE ε4 carriers may be due to the poorer survival among demented persons with APOE ε4 and heart disease, thus, some effect of selective survival cannot be excluded.

This seems to be the first study investigating the association between AF, HF, and CHD in midlife and in late-life and how they modulate the subsequent risk of clinically diagnosed dementia and AD. The CAIDE study design with its extensive study protocol for diagnosing dementia, as well as the utilization of the excellent register data available from multiple sources for defining the heart disease and dementia diagnoses, increases the reliability of these findings. It was also possible to control for several putative confounding factors in the

analyses. Some effect of survival bias on the results cannot be excluded, but if it does exist it would probably underestimate the association between heart diseases and dementia, not the opposite. Yet another possible limitation is that although the classification of heart diseases was based on self-report and register data, no clinical measurements of AF, HF, or CHD/atherosclerosis were available (e.g. ECG, heart ultrasound). However, the register data is based on diagnoses in the national hospital discharge register in Finland which includes information on in-patient sojourns in public hospitals, and therefore at least the more severe cases of heart diseases leading to hospitalization will be included in the study; the milder cases may have been undetected. In the secondary analyses including also the non-participants, the association between late-life AF and dementia became diluted. This may be due to a detection bias: there may be both undetected heart disease and especially dementia when relying on register data only. In the midlife analyses, the number of subjects with heart disease was limited, and thus could lead to insufficient power to detect associations.

6.4 METHODOLOGICAL ISSUES

6.4.1 CAIDE

6.4.1.1 Study population and design

The CAIDE study is based on population-based random samples of individuals that were investigated three times during the study. Participation rates were high, ranging from 77 % to 96 % at baseline, 72 % at first re-examination, and 63 % at second re-examination. The follow-up time of the study was long, on average 28 years at the second re-examination. The prospective population-based study design, the long follow-up time of the cohort, and the relatively high participation rates all increase the reliability of the findings from this study.

The baseline examinations were conducted in the framework of two large cardiovascular studies (the North Karelia Project and the FINMONICA study), neither of which was specifically designed to investigate cognitive functions or dementia. Thus, no information was available on the participants′ cognitive status at baseline. However, at the time of the midlife examination subjects were 39 to 64 years old, and it is most unlikely that they would have had dementia at that time. However, if there were individuals suffering from early signs of dementia already at the baseline examination, they would have probably not survived and participated in the re-examinations.

A random sample of survivors of the baseline survey participants was invited to participate in CAIDE in 1998. Information about the subjects who had died prior to this first re-examination was not available at the time of this study, and therefore, the possibility of some survival bias must be taken into consideration when interpreting the current results. At the general level, the results based on the CAIDE study are applicable to those subjects who survive until old age.

The CAIDE cohort is large enough to allow an investigation of risk factors that are rather prevalent in the population, such as smoking, pulmonary and heart diseases investigated here. However, the results of some subgroup analyses have to be interpreted with caution, because there might be false negative results due to insufficient power. In addition, the number of subjects with types of dementia other than AD was too small to allow any consideration of these kinds of dementia types (i.e. VaD) as outcomes in the analyses.

6.4.1.2 Risk factor measurements

The baseline risk factor measurements were made already at midlife, thus, the presence of preclinical dementia is unlikely to have influenced these measurements. However, some effect of preclinical dementia cannot be excluded in the analyses regarding the association between late-life pulmonary and heart diseases and dementia. Information on midlife smoking was based on self-report which may have caused some reporting bias. However, if some misreporting regarding information on smoking habits has occurred, it would most probably have been about the amount of smoking rather than the smoking status, and thus, ranking of individuals into different smoking categories, as conducted here, should be possible. Information on pulmonary diseases was also based on self-report. In particular, the COPD diagnoses in this study may also include some other chronic pulmonary diseases, probably mostly asthma, because particularly in the elderly the differentiation between COPD and asthma may be difficult, and patients may also display components of both diseases. Therefore, the analyses combining both pulmonary diseases were also carried out but they gave comparable results. Furthermore, the older a person becomes, the more are factors that can cause shortness of breath (e.g. heart diseases) which could have been falsely interpreted as a pulmonary condition, and this may have had some effect, especially on the late-life results. With respect to heart diseases, the self-reported and register data were combined in order to achieve as accurate information as possible on the diagnoses of heart diseases of the participants. However, some reporting bias regarding these analyses may still be possible.

6.4.1.3 Outcome measures

The screening criteria in the first re-examination was based on MMSE, and only subjects with MMSE ≤ 24 in the screening phase entered the clinical phase and underwent a more thorough investigation of cognitive functions. MMSE may have been sensitive enough to capture manifest AD, but the use of MMSE as the only screening criterion in the first re-examination may have resulted in an underdiagnosis of those dementia types in which memory deficits are not the main initial manifestation of the disease. In an attempt to improve the sensitivity to detect MCI and very mild dementia more criteria were used in the screening phase of the second re-examination. These may have also helped in detecting other dementia subtypes beyond AD at the second re-examination, as one of the screening criteria was based on report of cognitive decline by the informant, and not simply whether there was any memory impairment. It would have been ideal if all of the subjects had participated in both screening and clinical phases. However, the three phase protocol was probably adequate in sensitivity and specificity to detect AD since nearly half of all persons evaluated in the clinical phase of the first re-examination and 60 % of persons evaluated in the clinical phase of the second re-examination were nevertheless considered as being cognitively normal. Nearly all of those diagnosed with MCI or dementia underwent brain imaging in the differential diagnostic phase. Autopsy data were not available to confirm the clinical diagnoses, but a previous neuropathological study conducted in our clinic in Kuopio has shown that the accuracy of clinical AD diagnosis is good (96 % for probable AD and 86 % for possible AD) (Kosunen et al. 1996).

The diagnosis of MCI in the present study was essentially based on clinical judgement: the subjects did not fulfill the criteria for dementia, but had some subjective and objective cognitive impairment. Some cases of MCI and dementia may have been lost due to the MMSE cut-off score in the first re-examination. But this has not probably happened very frequently in the second re-examination because more screening criteria were used in an attempt to detect also milder forms of dementia and MCI. The first re-examination of the CAIDE study was designed

to detect dementia, and it is unclear how sensitive and specific this screening procedure was in identifying those persons with MCI. However, the prevalence of MCI in the first re-examination of the CAIDE study was similar to that of another population-based study conducted in the same region with a population of corresponding age, suggesting that the detection bias was minimal (Hanninen et al. 2002). During the second re-examination, the bias in detecting MCI was probably even more reduced.

6.4.1.4 Non-participation

Non-participation may have had some influence on these results. There was no information available for non-participants in the baseline surveys regarding risk factors or cognitive status. However, non-participation rates at baseline were rather low, ranging from 7 % in the cohort examined in 1972 to 17 % in the cohort examined in 1987 (Vartiainen et al. 1994). The main reasons for non-participation at baseline were: address information not up to date, temporarily away from home, or unable to participate; very few individuals actually refused to participate in the surveys (Puska et al. 1979).

The role of non-participation at follow-up could be evaluated to some extent. It is commonly known that persons with cognitive impairment are less likely to participate in these kinds of studies (Launer et al. 1994). The dementia diagnoses of non-participants of the re-examinations were sought from medical records of local hospitals and health care centres. At the time of studies III and IV, also register data on dementia diagnosis of the non-participants were available from three different national registers in Finland, and these were additionally investigated to obtain more diagnoses. In every study, the main analyses were repeated also among the whole study population including the non-participants with dementia diagnoses obtained from these other sources in order to estimate the effect of non-participation on the results. However, it is known that medical records usually underestimate the prevalence of dementia and so there still might be some cases of dementia missed among the non-participants. Nevertheless, as anticipated there were more demented individuals detected among the non-participants than among the participants in our study.

The non-participants were more often smokers at midlife than the participants. Thus, if the non-participants were at an increased risk of dementia and AD then the present results would not overestimate but rather underestimate the true effects of smoking on the risk of dementia and AD. The persons who did not participate in any re-examinations had also a higher systolic blood pressure, total serum cholesterol level, and BMI values in midlife than the participants. Thus, as expected, there were more persons with heart diseases (AF, HF, and CHD) among the non-participants (at midlife 10.0 % and at late-life 29.2 %) than among the participants (at midlife 8.8 % and at late-life 22.8 %). Therefore, if they were also at an increased risk of dementia this would result in an underestimation of the true impact of heart diseases on the risk of dementia and AD, not the opposite. With respect to pulmonary diseases, there were somewhat more persons with asthma and COPD among the non-participants (at midlife 6.8 %) than among the participants (at midlife 5.7 %) and if one assumes that they were also at an increased risk of cognitive impairment, then the present results would again represent an underestimation of the true effect. To evaluate the effect of non-participation the main analyses were repeated among the whole study population including also the non-participants in every study, but this gave comparable results in studies I and III. In study IV, the associations between late-life heart diseases and dementia became diluted when the whole cohort was analyzed. This was probably due to detection bias: regardless of utilization of the register data there may still be undetected heart disease and especially dementia among the non-participants.

6.4.1.5 Residual confounding

The possibility of bias due to confounding factors was addressed in all studies mainly by adjusting the analyses for possible confounders. In addition, some of the analyses were carried out separately in subgroups. There was information available on a wide range of sociodemographic, lifestyle, and health-related factors. However, there were factors about which no information was available, and some of the variables used may have been unable to capture all the dimensions of the phenomenon in question. Consequently, the possibility of residual confounding cannot be totally excluded.

6.4.2 Kaiser Permanente

6.4.2.1 Study population and design

The second study of the current project was based on a large multiethnic, retrospective study cohort of members of the Kaiser Permanente Medical Care Program of Northern California. The participants were clinically examined once at midlife during a voluntary health examination in 1978-1985. The dementia diagnoses of the subjects who were still alive and members of the health plan in 1994 were accessed from electronic medical record database between January 1st, 1994 and July 31st, 2008. The follow-up time of the study was long, on average 23 years. The main advantage of retrospective cohort studies in general is the quicker and less expensive access to large amounts of information on a variety of risk factors and outcomes. The large sample of 21 123 people of both men and women and various ethnic groups along with the long follow-up time of the cohort increases the reliability of the findings emerging from this study. Moreover, because smoking habits were measured in people aged 50 to 60 years, it is unlikely that subclinical dementia would have influenced the results. Although the sample is based on health plan members, Kaiser Permanente of Northern California covers more than one fourth of the population in the geographic areas it serves, and thus the members are representative of the sociodemographics of the local population (Krieger 1992)

6.4.2.2 Risk factor measurements

The baseline risk factor measurements were made already at midlife, thus, it is not likely that preclinical dementia would have been present then and consequently influenced these measurements. Information on midlife smoking was based on self-report, and thus, some reporting bias cannot be excluded.

6.4.2.3 Outcome measures

The large number of persons with dementia diagnoses in the cohort made it possible to evaluate the effect of midlife smoking on the risk of both AD and VaD. Since the diagnoses were obtained electronically from a medical record database, they are based on ICD-9-CM codes (the ICD-9-CM system is currently in use in the US for registering morbidity data). It was not possible to clinically screen all the participants for dementia; it is thus possible that a portion of the population may have had undiagnosed dementia. It is also likely that some of the AD or VaD cases were missed in those participants who had died before the onset of the ascertainment in 1994. Thus, some selective survival effect cannot be ruled out regarding the current results. However, it is known that both smoking (de Groot et al. 2004) and cognitive impairment (Stump et al. 2001) increase mortality. Accordingly, if it is assumed that among the deceased there were more smokers, and that they were more likely to be demented as well, then the present results would not overestimate but rather underestimate the true effects of smoking on the risk of dementia.

Neuropathological data regarding the diagnoses of AD and VaD in the Kaiser Permanente cohort was not available. The diagnostic criteria used in current clinical practice are known to have a bias towards AD due to the emphasis on memory impairment in the diagnosis of dementia. Therefore, there might be some cases of VaD or mixed dementia among those persons diagnosed with AD although the dementia subtypes were diagnosed by a neurologist or neuropsychologist in a memory clinic setting.

6.4.2.4 Residual confounding

To reduce the possibility of bias due to confounding factors, the analyses were adjusted for various possible confounders. In addition, analyses were carried out separately for those subjects with and without a stroke. A wide range of data on sociodemographic, lifestyle, and health-related factors was available for the study. However, it may be not be possible to control for some factors about which no information was available, and some of the variables used may have been unable to capture all the dimensions of the phenomenon in question. All covariates were measured with some inherent inaccuracy, thus leaving the possibility of some residual confounding effect.

7 Summary and Conclusions

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

1) Midlife smoking is associated with the risk of developing dementia and AD later in life especially among those individuals carrying the APOE ε4 allele. These results suggest that the association between smoking and AD may be complex and modulated by the genotype.

2) Midlife smoking is associated with an increased risk of dementia, AD, and VaD in a dose dependent manner; those individuals who smoke more than 2 packs per day in middle age are at the greatest risk of developing dementia. The deleterious effects of smoking on dementia risk seem to be the same for both genders and to span different ethnic groups.

3) COPD and asthma diagnosed in midlife are associated with the risk of cognitive impairment later in life. Pulmonary diseases diagnosed in late-life seem to have an inverse relationship with later cognitive impairment; however, this effect may be due to survival bias.

4) Heart diseases, especially atrial fibrillation, diagnosed in late-life are associated with a subsequent increased risk of dementia and AD later in life. Heart diseases diagnosed already in midlife do not appear to influence the later dementia risk.

8 Implications and Future Perspectives

The proportion of elderly people in the population is increasing all around the world, and consequently, age-related disorders are also becoming more common. Dementia is one disorder whose incidence is highly correlated with age. At the moment there is no curative treatment for this disorder. This represents a huge public-health and economic problem as the proportion of elderly persons with dementia is predicted to grow enormously during the next few decades. Thus, research into the risk factors and understanding in more detail the etiology of dementia and AD, the major form of dementia, are of great importance in the challenge of finding potential preventive strategies for the disease.

Recent findings showing that several lifestyle and health-related risk factors may increase the risk of dementia and AD has been of special interest because many of these risk factors are potentially modifiable. Moreover, it is now appreciated that these factors may affect the disease process in the brain already decades before the first clinical symptoms of dementia appear. These discoveries coincide with the findings from recent prospective cohort studies which have been able to follow-up their subjects for long periods of time. Because of the long preclinical phase of AD during which the neuropathological changes evolve in the brain, it is essential to examine the time before disease onset in order to reveal the actual factors which contribute to the triggering of the disease. The current project has investigated novel risk factors in two cohort studies with the baseline at midlife and a long follow-up time of over two decades for achieving this goal.

Regardless of the well founded awareness of the harmful effects of smoking, this habit is still quite common around the world, and even becoming more popular in some developing countries. The results of the current study indicate that in addition to increasing the risk of heart diseases, pulmonary diseases, and cancer etc. smoking also predisposes to dementia. Furthermore, the risk increase may be particularly high in individuals who are genetically susceptible to AD. There are also other factors that have been shown to increase the risk of dementia especially among the APOE ε4 carriers; for example physical inactivity, dietary fat intake, and frequent alcohol drinking at midlife are such factors. The current findings contribute to the growing body of evidence that the onset of dementia is a sum of genetic and environmental elements. The APOE ε4 carriers may be more vulnerable to environmental factors, and thus, lifestyle interventions may greatly modify dementia risk in these genetically susceptible individuals. The present findings also show that the harmful effects of smoking in regard to dementia risk are common to both men and women and in different ethnic groups. Promoting smoking cessation should be one of the major issues in the public education worldwide; it could help to prevent, or at least delay, the onset of dementia, and thus promote living a cognitively healthy life also into old age.

COPD and asthma are common pulmonary diseases causing substantial disability worldwide and COPD is one of the leading global causes of death. Although there is evidence that patients with COPD suffer greater cognitive impairment than in healthy persons, these diseases have not been widely studied with regard to the concomitant dementia risk. The current results indicate that COPD and asthma diagnosed in midlife may also increase the later risk of clinically diagnosed MCI and dementia. However, late-life pulmonary diseases do not predispose to the development of cognitive impairment. It is possible that augmentation of inflammation and neuronal damage due to the prolonged hypoxemia caused by these chronic diseases

contributes to the neurodegenerative process in the brain of subjects who will develop clinical dementia or MCI. There are studies which indicate that proper control of asthma in patients with cognitive impairment can improve some cognitive functions (Bozek et al. 2010, Bozek et al. 2011). Thus, the current findings emphasize the importance of good medical treatment of these pulmonary diseases also from the perspective of brain health and cognitive functioning.

CHD is also one of the leading causes of death around the world. HF is often the end stage of CHD and hypertensive heart disease and these are also the most common underlying disorders in AF. As more and more people survive into more advanced ages these heart conditions are becoming increasingly common. The influence on the dementia risk of comorbid diseases, which do not primarily directly affect the brain, has been recently acknowledged. This has opened a new avenue for discovering possible modifiable risk factors for dementia. The results of the current project suggest that the persons suffering from these heart diseases in late-life, especially from AF, are at an increased risk of developing dementia and AD as well. However, there was no relationship between these heart diseases diagnosed at midlife and the risk of dementia at late-life, except among the APOE ε4 carriers with heart failure who showed an increased risk of AD. Although this may reflect selective survival, it is also possible that the long follow-up time between the baseline and the late-life assessment of dementia may have enabled more effective treatment of hypertension and other cardiovascular risk factors in conjunction with beneficial changes in lifestyle during the follow-up years in persons with midlife heart diseases, resulting in a lowered dementia risk. These findings emphasize that dementia may result from various partly modifiable risk factors, not all necessarily affecting directly the brain itself. There is already evidence that treatment of vascular risk factors may slow the cognitive decline in AD (Deschaintre et al. 2009). There are also ongoing intervention studies focusing on several modifiable risk factors in individuals at risk of developing dementia. These studies will provide important information on the crucial question on how well optimal treatment of cardiovascular and other modifiable risk factors can affect the dementia risk and the progression rate of the disease. It has been estimated that a 5 year postponement in dementia onset would reduce the number of demented persons by 50 % (Brookmeyer et al. 1998). Thus, being able to at least delay the onset of dementia by treating the modifiable risk factors could have a tremendous effect on the prevalence of dementia in the future.

Previously, various lifestyle related factors have been related to the risk of dementia, but now, insights are being made into how these factors affect wellbeing and cognitive health in old age already start at least from middle age. There is already some evidence that different lifestyle behaviour patterns may be associated with different levels of risk for subsequent dementia, with a generally healthier lifestyle possibly being protective (Norton et al. 2012). Thus, one should pay attention to lifestyle already at midlife, because the choices made at that time may have long-lasting effects, and may also affect one's risk of developing dementia in old age. With regard to prevention, this is good news. The previous, almost fatalistic, view was that AD was mainly induced by genetic risk factors and age. However, recent knowledge about the environmental risk factors of the disease provides hope also for genetically susceptible individuals; the risk of developing dementia may be lowered by adopting a healthy lifestyle. The exact mechanisms of action which mediate the increased disease risk contributable to lifestyle and comorbid diseases are not currently known, and these will need to be clarified in future studies.

9 References

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Minna Rusanen

Smoking, Pulmonary and Heart Diseases and the Risk of Cognitive Impairment and Dementia: An Epidemiological Approach

As more people are surviving into more advanced ages, prevention of dementia is now a major public health challenge. Recent findings showing that several lifestyle and health-related risk factors may increase the risk of for dementia and its major cause, Alzheimer's disease (AD), has been of special interest because many of these risk factors are potentially modifiable. This thesis investigated putative risk factors for dementia and AD that have not been previously indepth studied: smoking and common pulmonary and heart diseases, in two cohort studies with the baseline at midlife and a long follow-up time of over two decades.

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