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Lifestyle-Related Risk Factors in Dementia and
Mild Cognitive Impairment:
A Population-Based Study

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To my parents

ABSTRACT - English

As an increasing number of individuals survive into advanced age, dementia and milder cognitive impairments takes on growing public health importance. The aetiology of dementia and Alzheimer's disease (AD), which is the most common cause of dementia, is considered to be multifactorial, resulting from both genetic and environmental factors. The present thesis project aimed at obtaining a comprehensive understanding of the role of lifestyle-related factors in the development of dementia and cognitive impairment. Special attention was paid to possible interactions between lifestyle-related and genetic risk factors. The general hypothesis was that a healthy lifestyle could reduce the risk of dementia and cognitive impairment.

All five studies were based on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) project. The participants in the CAIDE project were derived from four independent population-based random samples studied within the framework of the North Karelia Project and the FINMONICA study in 1972, 1977, 1982 or 1987. A random sample of 2000 individuals aged 65-79 years and living in two geographically defined areas in Kuopio and Joensuu in eastern Finland were invited for the re-examination in 1998, and altogether 1449 people (73 %) participated.

In *study 1*, obesity at midlife was associated with an increased risk of dementia and AD. Midlife obesity, high cholesterol, and high systolic blood pressure were all significant risk factors for dementia with ORs of around 2 for each parameter, and they increased the risk additively.

In *study 2*, we observed a U-shaped association between midlife alcohol drinking and the risk of mild cognitive impairment (MCI) in late-life, so that the participants who did not drink alcohol, as well as those who drank alcohol frequently, had a two-fold risk of having MCI when compared with those participants who drank alcohol infrequently. The presence of the apolipoprotein E (ApoE) $\epsilon 4$ allele modified the association between alcohol drinking and dementia: ApoE $\epsilon 4$ carriers showed an increased risk of dementia with increasing alcohol drinking frequency, whereas this was not the case for the ApoE $\epsilon 4$ non-carriers.

In *study 3*, we investigated the relationship of midlife alcohol drinking to cognitive functions in late-life among the non-demented individuals. The participants who did not drink alcohol at midlife, had poorer performance compared to infrequent and frequent drinkers in episodic memory, psychomotor speed, and executive function in late-life.

In *study 4* low income level in late-life but not at midlife was related to the risk of dementia. Dementia was also associated with decreasing income level from midlife to old age. Low educational level and the ApoE $\epsilon 4$ allele independently increased the risk of dementia.

In *study 5* we examined whether the association between education and dementia was due to the presence of unhealthier lifestyles or more cardiovascular risk factors among the less educated persons. High education was associated with a lower risk of dementia and AD, and it remained unchanged after adjustments for a wide range of lifestyle factors.

In summary, this set of studies showed that unhealthy lifestyle-related factors at midlife, such as obesity, hypertension and hypercholesterolemia increase the risk of developing dementia and AD later in life. Especially among ApoE $\epsilon 4$ allele carriers, alcohol drinking increases the risk of dementia. On the other hand, in non-demented individuals, alcohol drinkers exhibit better cognitive performance compared to abstainers. However, it is not clear whether this association is causal, or what is the optimal level of alcohol consumption to achieve the best cognitive function. High education is associated with a decreased risk of dementia whereas a high income level at midlife is not a contributory factor. A reduction in relative income level between midlife and late-life might well be a consequence of the dementing disease process. Educated persons may have a greater cognitive reserve that leads to a postponement of the clinical manifestation of dementia. The unhealthy lifestyle options may independently contribute to the depletion of this reserve or directly induce the pathologic processes underlying dementia and AD.

Medical Subject Headings: alcohol drinking, Alzheimer disease, apolipoprotein E, cohort studies, dementia, educational status, epidemiology, life style, obesity, risk factors, socioeconomic factors

ABSTRAKT – Svenska

När allt fler individer lever tills hög ålder, är demens en allt viktigare utmaning för folkhälsan. Demenssjukdomarnas etiologi anses vara multifaktoriell, och den påverkas av både genetiska och miljöfaktorer. Denna doktorsavhandling syftade till en vidare förståelse om vilken roll livsstilsrelaterade faktorer spelar i utvecklingen av demens och kognitiv nedsättning. Speciellt fokuserades på potentiella interaktioner mellan livsstils- och genetiska riskfaktorer. Den allmänna hypotesen var att en hälsosam livsstil kan minska risken för demens och kognitiv nedsättning.

Alla fem studierna var baserade på Cardiovascular Risk Factors, Aging and Dementia (CAIDE) projekt. Deltagarna i CAIDE projekt kom från fyra oberoende populations-baserade slumpmässiga urval som studerades inom Nord Karelia Projektet och FINMONICA studien i 1972, 1977, 1982 eller 1987. Ett slumpmässigt urval av 2000 individer i åldrarna 65-79 år som bodde på två geografiska områden i Kuopio och Joensuu i Östra Finland kallades till en uppföljningsexamination i 1998, och sammanlagt 1449 personer (73 %) deltog.

I *studie 1* visades att fetma i medelåldern hade samband med en ökad demensrisk. Fetma, hög kolesterol, och högt systolisk blodtryck i medelåldern var alla signifikanta riskfaktorer för demens. Alla dessa faktorer fördubblade risken för demens, och tillsammans ökade de här faktorerna demensrisken på ett additivt sätt.

I *studie 2* observerade vi att de deltagare som inte drack alkohol i medelåldern samt dem som drack alkohol ofta hade en tvåfaldig risk för lindrig kognitiv nedsättning senare i livet jämfört med personer som drack alkohol sällan. Genen apolipoprotein E (ApoE), $\epsilon 4$ allele modifierade sambandet mellan alkoholdrickande och demens: ApoE $\epsilon 4$ bärare hade ökad risk för demens ju oftare de drack alkohol, men de som inte var ApoE $\epsilon 4$ bärare hade inte något sådant samband.

I *studie 3* undersökte vi sambandet mellan alkoholdrickandet i medelåldern och kognitiva funktioner senare i livet hos personer som var icke-dementa. Deltagare som inte drack alkohol i medelåldern hade lägre prestationsförmåga jämfört med dem som drack alkohol sällan eller ofta när det gäller episodiskt minne, psykomotorisk snabbhet, och exekutiv funktion senare i livet.

I *studie 4* fann vi att låg inkomst i senare delen av livet var associerad med demens, medan låg inkomst i medelåldern inte var det. Demens var också kopplat till sjunkande inkomstnivå mellan medelåldern och hög ålder. Både låg utbildning och ApoE $\epsilon 4$ ökade risken för demens oberoende av varandra.

I *studie 5* undersökte vi om sambandet mellan utbildningsnivå och demens kan förklaras av att personer med låg utbildning ofta har ohälsosammare livsstilar och mera kardiovaskulära riskfaktorer. Hög utbildning var associerat med lägre risk för demens och Alzheimers sjukdom, och sambandet blev oförändrat när man tog hänsyn till effekten av flera livsstilsfaktorer.

Sammanfattningsvis, ohälsosamma livsstilsrelaterade faktorer i medelåldern, inklusive fetma, hypertoni och hyperkolesterolemi ökar risken för utveckling av demens och Alzheimers sjukdom senare i livet. Särskilt bland ApoE $\epsilon 4$ bärare ökar alkohol drickande risken för demens. Å andra sidan, hos icke-dementa personer, har de som dricker högre kognitiv förmåga jämförd med dem som inte dricker alkohol. Ändå är det inte tydligt om sambandet är kausalt, och vad som skulle vara en lagom nivå av alkohol konsumtion för bästa kognitiva förmåga. Hög utbildning har samband med minskad risk för demens medan hög inkomst i medelåldern inte har det. Minskning i den relativa inkomstnivån mellan medelåldern och hög ålder kan dock vara konsekvens av demsens sjukdomsprocess. Personer med hög utbildning kan ha större kognitiv reserv som leder till försening av klinisk manifestation av demens. Ohälsosamma livsstilsval kan på ett oberoende sätt bidra till bortfall av denna reserv eller direkt påverka den patologiska sjukdomsprocessen.

TIIVISTELMÄ - Suomi

Yhä useammat henkilöt elävät vanhuusiikään saakka, ja tämän vuoksi dementian ja lievemmän kognitiivisen heikentymisen merkitys kansanterveydelle kasvaa. Dementian, ja erityisesti Alzheimerin taudin (AT), joka on tavallisin dementoiva sairaus, etiologiaa pidetään monitekijäisenä, ja siihen vaikuttavat sekä geneettiset että ympäristötekijät. Tämän väitöskirjatutkimuksen tavoitteena oli ymmärtää elintapatekijöiden vaikutus dementian ja kognitiivisen heikentymisen kehittymisessä. Erityisesti huomioitiin elintapojen ja geneettisten riskitekijöiden mahdolliset yhdysvaikutukset. Yleisenä lähtöoletuksena oli että terveelliset elintavat voisivat vähentää dementian ja kognitiivisen heikentymisen riskiä.

Kaikki viisi osatutkimusta pohjautuivat Kardiovaskulaariset riskitekijät, Ikääntyminen ja Dementia (CAIDE) projektiin. CAIDE –projektin osallistajat olivat peräisin neljästä itsenäisestä väestöpohjaisesta satunnaisotoksesta henkilöitä, jotka oli tutkittu osana Pohjois-Karjala projektia ja FINMONICA tutkimusta vuosina 1972, 1977, 1982 tai 1987. 2000 henkilön satunnaisotos 65-79 vuotiaita Kuopion ja Joensuun aluella asuvia henkilöitä kutsuttiin seurantatutkimukseen 1998, ja yhteensä 1449 (73 %) heistä osallistui.

Tutkimuksessa 1 keski-ikä lihavuus oli yhteydessä suurentuneeseen dementian ja AT:n riskiin. Keski-ikä lihavuus, korkea kolesteroli ja korkea systolinen verenpaine olivat kaikki merkittäviä dementian riskitekijöitä. Jokainen näistä tekijöistä kaksinkertaisti dementian riskin, ja yhdessä ne lisäsivät dementian riskiä additiivisesti.

Tutkimuksessa 2 havaitsimme että henkilöillä jotka eivät juoneet alkoholia keski-ikässä, sekä henkilöillä jotka joivat alkoholia usein, oli kaksinkertainen riski myöhäsiän lievään kognitiiviseen heikentymiseen verrattuna niihin henkilöihin jotka joivat alkoholia harvoin. Apolipoproteiini E (ApoE) $\epsilon 4$ alleeli muunsi dementian riskiä: ApoE $\epsilon 4$ kantajilla dementian riski kasvoi tiheimmän alkoholinjuomisen myötä.

Tutkimuksessa 3 selvitimme keski-ikä alkoholin juomisen vaikutusta myöhäsiän kognitiivisille toiminnoille niillä henkilöillä, joilla ei ollut dementiaa. Henkilöt, jotka eivät juoneet alkoholia keski-ikässä suoriutuivat huonommin kuin harvoin tai usein alkoholia juovat henkilöt episodista muistia psykomotorista nopeutta ja eksekutiivisia toimintoja mittaavissa testeissä myöhäsiässä.

Tutkimuksessa 4 matala tulotaso myöhäsiässä oli yhteydessä dementiaan, mutta keski-ikä tulotasolla ei ollut vaikutusta. Tulotason lasku keski-ikästä myöhäsiikään oli myös yhteydessä dementian riskiin. Alhainen koulutustaso ja ApoE $\epsilon 4$ alleeli kumpikin itsenäisesti lisäsivät dementian riskiä.

Tutkimuksessa 5 selvitimme johtuuko koulutuksen ja dementian välinen yhteys siitä, että vähemmän koulutetuilla on epäterveellisemmät elintavat ja enemmän kardiovaskulaarisia riskitekijöitä. Korkea koulutus oli yhteydessä vähentyneeseen dementian ja AT:n riskiin, ja tulos pysyi muuttumattomana vaikka lukuisten elintapatekijöiden vaikutus otettiin huomioon.

Tiivistetysti, tutkimuksemme osoitti että keski-ikä epäterveelliset elintapatekijät, kuten lihavuus, korkea verenpaine ja korkea kolesteroli lisäävät myöhäsiän dementian ja AT:n riskiä. Erityisesti geneettisesti alttiilla henkilöillä alkoholin juominen lisää dementian riskiä. Toisaalta, ei-dementoituneiden joukossa niillä jotka juovat alkoholia on parempi kognitiivinen suoritustaso raittiisiin verrattuna. On kuitenkin epäselvää onko kyseessä syy-seuraussuhde, ja mikä olisi sopiva alkoholimäärä kognitiivisten toimintojen kannalta. Korkea koulutus on yhteydessä vähentyneeseen dementian riskiin kun taas keski-ikä korkea tulotaso ei ole. Tulotason aleneminen keski-ikä ja myöhäsiän välillä saattaakin olla dementoivan tautiprosessin seuraus. Korkeasti koulutetuilla henkilöillä voi olla suurempi kognitiivinen reservikapasiteetti, mikä johtaa dementian ilmentymisen myöhäistymiseen. Epäterveelliset elintavat voivat vaikuttaa joko itsenäisesti tämän reservin vähenemiseen tai suoraan patologiisiin tautiprosesseihin.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications:

- I. Kivipelto M, **Ngandu T**, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, Helkala E-L, Tuomilehto J, Soininen H, Nissinen A. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Archives of Neurology* 2005;62:1556-1560.
- II. **Anttila T**, Helkala E-L, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B, Soininen H, Tuomilehto J, Nissinen A, Kivipelto M. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population-based study. *British Medical Journal* 2004;329:539-542.
- III. **Ngandu T**, Helkala E-L, Soininen H, Winblad B, Tuomilehto J, Nissinen A, Kivipelto M. Alcohol drinking and cognitive functions: Findings from the Cardiovascular Risk factors, Aging and Dementia (CAIDE) study. (Manuscript)
- IV. **Anttila T**, Helkala EL, Kivipelto M, Hallikainen M, Alhainen K, Heinonen H, Mannermaa A, Tuomilehto J, Soininen H, Nissinen A. Midlife income, occupation, APOE status, and dementia: a population-based study. *Neurology* 2002;59:887-893.
- V. **Ngandu T**, von Strauss E, Helkala E-L, Winblad B, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Education and dementia: what lies behind the association? Results from the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study. (Manuscript)

NB Tiia Anttila has after marriage changed her family name to Ngandu.

ABBREVIATIONS

AD	Alzheimer's disease
ApoE	Apolipoprotein E
BMI	Body mass index
CAIDE	Cardiovascular Risk Factors, Aging and Dementia study
CI	Confidence interval
DBP	Diastolic blood pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition
FINMONICA	Finnish part of Monitoring Trends and Determinants in Cardiovascular Disease
ICD-10	International Classification of Diseases, 10 th revision
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
OR	Odds ratio
RR	Risk ratio
SBP	Systolic blood pressure
VaD	Vascular dementia

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- Dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2006
- Original publications

INTRODUCTION

Definition and Occurrence of Dementia

Dementia is a syndrome that is defined by impairments in memory and other cognitive functions that are severe enough to cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.¹ Probably dementia has existed since the dawn of mankind, even though the concept of what dementia is, and how it should be defined has evolved over the years.² Dementia is a syndrome with many causes, and its diagnosis is based on fulfilment of a set of criteria. Several diagnostic classifications exist, with the most commonly used being those of American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, IV edition (DSM-IV),¹ as well as World Health Organization's (WHO) International Classification of Diseases, 10th revision (ICD-10).³ The core of the different classification systems is similar, but they differ from each other in some details and do not necessarily identify the same persons as being demented.⁴

Dementia is estimated as affecting approximately 6 % percent of the population aged 65 years and older, with the prevalence increasing exponentially with age, being 40 to 70 % among those aged 95 and above.^{5 6} As an increasing number of individuals survive into these advanced ages,⁷ also the number of demented persons is expected to increase. It has been estimated that the prevalence of dementia will quadruple in the next 50 years if no means to combat the disease are found.⁸⁻¹⁰ The treatments available today do not cure dementia, but at best they relieve symptoms and may slow down the progression. The medical, social and economic problems related to dementia are important and they will represent an increasing challenge for public health in the coming years.^{11 12}

Alzheimer's disease

A hundred years ago, Alois Alzheimer described a disease that later became known as Alzheimer's disease (AD).¹³ Alzheimer's description was based on a patient called Auguste D, a 51-year-old woman who had shown progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence. At autopsy, he noted plaques, neurofibrillary tangles and arteriosclerotic changes in her brain. After these first descriptions

of the neuropathologic hallmarks of AD, the disease was considered to be a rarity until the 1970's. Today, it is estimated to account for 60 to 70 % of all incident dementia cases.¹⁴

AD is a slowly progressive disease that most often starts with episodic memory impairment. Even before a diagnosis of AD can be considered, the patients with preclinical AD exhibit deficits in several cognitive functions, including episodic memory, executive function, perceptual speed, verbal ability, visuospatial ability, and attention.¹⁵ Cognitive function declines over time, and the diagnosis of AD can be considered when the patient has impairments in memory and at least in one other cognitive function (aphasia, apraxia, agnosia, executive dysfunction), severe enough to cause impairment in social or occupational functioning. In advanced AD, common symptoms include also confusion, behavioural and gait disturbances, and the patients are increasingly dependent on others in activities of daily living.

The diagnosis of AD is essentially a clinical one, and it is based on a typical clinical picture and findings. The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD are often used in research.¹⁶ These criteria for probable AD include 1) dementia established by clinical examination, and documented by a standard test of cognitive function, and confirmed by neuropsychological tests, 2) significant deficiencies in two or more areas of cognition, 3) progressive deterioration of memory and other cognitive functions, 4) no loss of consciousness, 5) onset from age 40 to 90, typically after 65, 6) no other diseases or disorders that could account for the loss of memory and cognition.

At the moment there is no single simple and reliable diagnostic tool to detect AD in its early phases. However, cumulative information from several measures can be used to support the clinical diagnosis. An interview with a family member, and performance on neuropsychological tests do provide useful diagnostic information.^{17 18} Atrophy in the medial temporal lobe, in hippocampus and in the surrounding regions in structural neuroimaging, and reduced blood flow and glucose metabolism in functional neuroimaging is supportive of the diagnosis of AD.¹⁹ In addition, biomarkers in cerebrospinal fluid including decreased levels of β -amyloid₁₋₄₂, and elevated levels of total tau and phosphorylated tau support the diagnosis of AD.²⁰ The average duration of manifest AD is from 4 to 20 years. Pathologically AD is characterised by diffuse cerebral atrophy associated with β -amyloid neuritic plaques,

neurofibrillary tangles, and angiopathy. A higher density of senile plaques and neurofibrillary tangles in specific brain regions together with the presence of a clinical history of AD type of dementia confirm the diagnosis of AD.²¹

Other dementing diseases

After AD, the second most common dementia is vascular dementia (VaD). VaD includes clinical forms of dementia caused by ischemic, or hemorrhagic cerebrovascular disease or by ischemic-hypoxic brain lesions.²² Especially among aged persons, both neurodegenerative and vascular changes are present and it is difficult to determine whether the dementia is due to AD or VaD.²³ In fact, pure AD and pure VaD may be rare entities at the opposite ends of a continuum, whereas 'mixed' dementia may be more common.²⁴

Other dementing disorders are frontotemporal degeneration affecting individuals younger than 70 years, Lewy body disease where AD pathology is common especially in the elderly patients, and Parkinson's disease with dementia. In addition a number of other disorders may lead to dementia, for example alcohol related dementia, dementia due to normal pressure hydrocephalus, and HIV-related dementia. The focus of this thesis is on dementia as a whole and specifically AD, and therefore other dementias will not be discussed.

Cognitive Impairment

Several cognitive functions, such as psychomotor speed, executive function, and episodic memory decline with normal aging. Other functions, including semantic memory remain fairly intact.^{25 26} Differences in the cognitive functions between individuals become greater with aging.^{27 28} The identification of the determinants of these differences has been on the focus of much research.

Dementia is thought to be preceded by a state of cognitive decline greater than that related to normal aging but not severe enough to permit a diagnosis of dementia. This state has been called by many names, and been defined with a variety of criteria.²⁹⁻³¹ The concept of mild cognitive impairment (MCI) has become increasingly popular in the last years. It is thought to identify persons at high-risk for developing AD.^{32 33} However, controversies exist about how best to define MCI. Recently an expert panel recommended a consensus criteria for MCI that included: 1) the person is neither normal nor demented; 2) there is evidence of cognitive

deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits and; 3) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired.³⁴

MCI is not a disease in itself but it can be considered as a clinical and research entity. There has been much interest in MCI due to the fact that it has been thought to be a preclinical state of AD. However, MCI is more than simply early-AD; the aetiology of MCI is probably heterogeneous: both degenerative, vascular, metabolic, traumatic, psychiatric and possibly even other reasons may lie behind the symptoms.³⁴ Subclassifications of MCI according to the clinical presentation of the cognitive deficit have been proposed: amnesic MCI, multiple cognitive domain slightly impaired MCI, and single nonmemory domain MCI.³⁵ These sub-categories might be related to different aetiologies behind the cognitive impairment. Many persons with MCI develop AD over a period of a few years, but recent studies have indicated that the evolution is heterogeneous, as some persons remain stable and some even improve over time.^{36 37}

As the definition of cognitive impairment syndromes without dementia, including MCI has varied greatly in the earlier research, it is difficult to compare information across studies. Therefore the epidemiology of cognitive impairment including its occurrence and risk factors has remained an enigma. Estimates of prevalence of syndromes of cognitive impairment without dementia vary from around 3 % using the strict criteria for amnesic MCI, up to 20 % when a more broad definition of cognitive impairment has been used.³⁰ As MCI is thought to present a transitional state between normal cognition and dementia, one could expect similar risk factors to be relevant for both MCI and dementia. Accordingly, it has been proposed that advanced age, low education and the presence of ApoE ϵ 4 would be associated with an increased risk of MCI.³⁸ Also low performance on cognitive tests, cortical atrophy and infarcts in magnetic resonance imaging, depression and African American race are associated with the development of MCI.³⁹ Further, both hypertension and hypercholesterolemia at midlife have also been proposed to increase the risk of MCI.⁴⁰

Aetiology of Dementia and Alzheimer's Disease

The aetiology of dementia and AD are considered to be multifactorial, resulting from an interaction between genetic susceptibility and environmental factors. A huge body of literature exists on the risk factors of dementia and AD. An extensive evidence-based systematic review on these risk factors was prepared for the Swedish Council on Technology Assessment in Health Care (SBU) by the dementia - risk factors working group.⁴¹ The review included studies on risk factors published between 1987 and 2004. The evidence grading was based on the criteria for internal validity and causality of individual studies, and on the consistency and amount of accumulated evidence. Table 1 presents a summary of the main proposed risk factors and protective factors for dementia and AD. In the present work, a brief overview of the main identified risk factors is given. A detailed review is presented on the role of those lifestyle-related risk factors that are central to the present thesis, namely: obesity, alcohol drinking, education and socioeconomic factors.

Age, sex and family history

For many years, the only confirmed risk factors for sporadic dementia and AD were age and family history. Both prevalence and incidence of dementia increase with advanced age.^{5 6} After the age of 65, its occurrence doubles every five years. Dementia may be more frequent among women than among men, especially in the very old.¹⁴ The risk of dementia and AD has been shown to be increased among persons with a family history of dementia,⁴²⁻⁴⁴ though contradictory results exist as well.⁴⁵

Genetic risk factors

The vast majority of all AD is so-called late-onset or sporadic AD. For the late-onset AD, no single gene mutation has been identified as being responsible for the disease. In some rare families, AD occurs as a single-gene autosomal dominant trait. Three causative genes have been identified in these cases of familial early-onset AD: the amyloid precursor protein (APP) gene in chromosome 21, the presenilin 1 gene in chromosome 14, and the presenilin 2 gene in chromosome 1. These genes account for less than 2 % of all cases of AD.⁴⁶ Patients with trisomy 21 (Down syndrome) are at an increased risk of AD since they carry an extra copy of the APP gene.⁴⁷

Table 1. Evidence for the main proposed risk factors for dementia and AD

DEMENTIA	AD
<p>RISK FACTORS</p> <p>Strong evidence: Age</p> <p>Moderate evidence: ApoE ε4 allele Familial aggregation Midlife hypertension Diabetes</p> <p>Limited evidence: Occupational exposure</p> <p>Insufficient evidence: Smoking Late-life hypertension Obesity Cardiovascular disease High homocysteine Inflammatory factors Head trauma Aluminium Dietary factors Folate/ vitamin B12 Depression Low socioeconomic status</p>	<p>RISK FACTORS</p> <p>Strong evidence: Age ApoE ε4 allele</p> <p>Moderate evidence: Midlife hypertension Familial aggregation</p> <p>Limited evidence: Midlife hypercholesterolemia Occupational exposure</p> <p>Insufficient evidence: Smoking Diabetes Late-life hypertension Obesity Cardiovascular disease High homocysteine Inflammatory factors Head trauma Aluminium Dietary factors Folate/ vitamin B12 Depression Low socioeconomic status</p>
<p>PROTECTIVE FACTORS</p> <p>Moderate evidence: High education Leisure time activities Antihypertensive drugs</p> <p>Limited evidence: Moderate alcohol drinking</p> <p>Insufficient evidence: Non-steroidal anti-inflammatory drugs Statins Social network</p>	<p>PROTECTIVE FACTORS</p> <p>Moderate evidence: High education Leisure time activities</p> <p>Limited evidence: Antihypertensive drugs Moderate alcohol drinking</p> <p>Insufficient evidence: Non-steroidal anti-inflammatory drugs Statins Social network</p>

Modified from the report of the Dementia - Risk Factors Working Group for the the Swedish Council on Technology Assessment in Health Care (SBU).⁴¹

The apolipoprotein E ε4 allele (ApoE ε4) is at the moment the only genetic risk factor for AD that is important for the general population. The human ApoE gene has three different alleles: in addition to ε4 allele, there are ε2 and ε3 alleles, with the ε3 being the most common, and the ε2 is the rarest. There is some variation in ApoE allele distribution across the world.⁴⁸ In

Finland, the $\epsilon 4$ frequency is higher than in many Western countries. More than 30 % of our study population are carriers of either one or two $\epsilon 4$ alleles. The first evidence that ApoE $\epsilon 4$ carriers had an increased risk of late-onset familial and sporadic AD appeared in 1993.⁴⁹ Subsequently the finding has been replicated in both clinical and population settings, and several meta-analyses have been performed.^{50 51} ApoE $\epsilon 4$ has been shown to intensify all the biochemical disturbances characteristic of AD including A β deposition, tangle formation, neuronal cell death, oxidative stress, synaptic plasticity and dysfunctions in lipid homeostasis and cholinergic signalling.⁵² ApoE $\epsilon 4$ has been proposed to modify the effects of various vascular and lifestyle related factors for cognitive functioning and dementia, so that the ApoE $\epsilon 4$ carriers might be more vulnerable to various adverse environmental factors (eg. alcohol, blood pressure, vitamin B12).⁵³⁻⁵⁵

Psychosocial factors and physical activity

In the recent years, extensive work has been done on the role of psychosocial factors, and physical activity for the development of dementia. There is some evidence that an active and socially integrated lifestyle may reduce the risk of dementia and cognitive impairment.⁵⁶ Specifically, rich social network,⁵⁷ being married,^{58 59} leisure time cognitive, social or mental activities,⁶⁰⁻⁶² and regular physical activity^{63 64} have been associated with a decreased risk of dementia and AD. It has even been proposed that non-intellectually stimulating activities, like watching television, might actually increase the risk of AD.⁶⁵ Depression and depressive symptoms occur frequently during the pre-clinical stages of AD, but whether depression in itself increases the risk of developing AD remains controversial.⁶⁶

Inflammatory factors, head trauma and aluminium

It has been suggested that inflammatory markers might be associated with an increased risk of dementia, and non-steroidal anti-inflammatory drugs with a decreased risk of dementia but so far the evidence is scanty.⁶⁷⁻⁶⁹ Head trauma has been suggested to increase the risk of dementia but there are contradictory findings.⁷⁰ Similarly, there is not sufficient evidence to state whether aluminium is associated with dementia.⁷¹

Vascular risk factors

Dementia shares many risk factors with cardiovascular diseases. There is fairly strong epidemiological evidence that hypertension at midlife and possibly also in late-life is

associated with an increased risk of all types of dementia, as well as AD and VaD.⁷²⁻⁷⁶ Blood pressure seems to decline in the years before the diagnosis of dementia.^{75 77} This may explain the inverse association between blood pressure and risk of dementia found in some cross-sectional studies. Further, antihypertensive drug use may protect from developing dementia,^{54 78} though the evidence from randomised controlled trials is not equivocal.⁷⁹⁻⁸¹ Hypercholesterolemia at midlife has been shown to be associated with an increased risk of dementia and AD,^{72 82} but one study addressing the relation of long-term cholesterol levels to subsequent AD could detect no association⁸³. Shorter term follow-up studies or cross-sectional studies have reported no association or even an inverse association.^{84 85} Further, some studies have pointed to a beneficial effect of statin treatment on the dementia,^{86 87} but the evidence is insufficient and contradictory at the moment.^{85 88-90}

Diabetes mellitus seems to increase the risk of developing dementia.⁹¹⁻⁹³ The evidence on the association between diabetes and AD specifically are somewhat inconsistent but generally supportive of a positive association.⁹³⁻⁹⁵ Smoking was earlier in cross-sectional studies proposed to protect from dementia and AD, but these findings have probably been attributable to selective survival. Recent large prospective studies have either found no association between smoking and dementia, or an increased risk of dementia in smokers.^{45 96 97} High levels of homocysteine, and low levels of folate, and vitamin B12 might be related to an increased risk of AD.⁹⁸⁻¹⁰⁰ Population-based studies have pointed to a protective effect of hormone replacement therapy for dementia, but the Women's Health Initiative Memory Study randomized trial did not support these findings, and at the moment hormone replacement therapy is not recommended as a means of preventing dementia.^{101 102}

Obesity and nutrition

The prevalence of obesity is on the increase all over the world, and it now constitutes a major global public health problem.¹⁰³ It has been estimated to be the second most important cause of mortality after smoking in the United States.¹⁰⁴ Obesity is related to several vascular diseases, but the association between obesity and the risk of dementia has not been extensively studied.

Several studies have shown that weight loss is a common feature in AD patients,^{105 106} and both low fat-free soft tissue mass and low fat mass have been associated with poorer cognitive

function.¹⁰⁷ Weight loss has been proposed to be more pronounced among the ApoE ε4 allele carriers.¹⁰⁸ The observation that AD patients have a lower weight and body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) than the control patients has led to the assumption that low BMI could be a risk factor for dementia. However, the weight loss seems to occur during the pre-clinical phases of dementia. Findings from the Honolulu-Asia Aging Study recently showed that there was a greater weight loss in late-life among those persons that developed dementia, AD or VaD,¹⁰⁹ and similarly an earlier population-based study from Southern California showed a significant decline in weight among those individuals that subsequently developed AD.¹¹⁰ The Religious Orders study showed that declining BMI was associated with both increased risk of AD and increased rate of cognitive decline.¹¹¹ Further, the results from the French population-based Personnes Agées QUID (PAQUID) study with a follow-up time of eight years suggested that a low BMI would be an early sign of dementia rather than a risk factor as such.¹¹²

The few long-term follow-up studies that have addressed the question about obesity and the risk of dementia have yielded somewhat conflicting results. Table 2 summarises the results of the main prospective studies on BMI and dementia. A higher cardiovascular metabolic risk factor burden, including BMI, random postload glucose, DBP and SBP, subscapular skinfold thickness and total cholesterol, in middle aged men, increased the risk of dementia and VaD, but not AD, 25 years later in the Honolulu-Asia Aging Study.¹¹³ However, another study conducted in Japan detected no association between midlife BMI and VaD or AD 25 to 30 years later in a cohort including mostly women.¹¹⁴ In contrast, a recent Swedish cohort study found that women who were overweight at the age 70, 75 or 79 had an increased risk of dementia and AD 9 to 18 years later.¹¹⁵ Two large studies using dementia diagnoses from registries have shown that high BMI at midlife increased the risk of dementia,^{116 117} and that even low midlife BMI was associated with an increased risk of dementia.¹¹⁶

The effect that obesity may have on dementia could be to some extent due to nutrition. Only a few studies have investigated the association between dietary fat intake and the risk of dementia. It has been reported that a diet rich in saturated fat and cholesterol might increase the risk of dementia whereas an intake of polyunsaturated fatty acids and fish might be protective.^{118 119} However, contradictory findings exist as well.¹²⁰ Interestingly, it has also been reported that high fat and cholesterol intakes might be risk factors for AD, especially among the ApoE ε4 carriers.^{121 122}

Table 2. The prospective studies examining the association between body mass index and dementia

<i>Study</i>	<i>Study population</i>	<i>Study design</i>	<i>Body Mass Index</i>	<i>Covariates</i>	<i>Outcome and results</i>
Kalmijn et al., 2000 ¹¹³ Honolulu-Asia Aging Study, USA	N=3734, mean age 53 years, Japanese-American men	Population-based study, 25 years follow-up	Continuous	Age, education	1-SD increase in midlife BMI was related to an increased risk of dementia and VaD but not to AD
Gustafson et al., 2003 ¹¹⁵ Gothenburg study, Sweden	N=266 women, 166 men, 70 years	Population-based study, 9-18 years follow-up	BMI at the age of 70, 75 and 79 years, continuous	DBP, cardiovascular disease, smoking, socioeconomic status, antihypertensive drugs	BMI (per unit) at age 70, 75, and 79 was related to an increased risk of dementia and AD among women at 79 to 88 years. Ns for VaD , and for men.
Nourhashemi et al., 2003 ¹¹² PAQUID study, France	N=3646, 65+ years, living at home	Population-based study, 8 years follow-up	BMI < 21, 21-22, 23-26 and ≥ 27 kg/m ²	Age, sex, age-sex interaction, education, alcohol and tobacco consumption	BMI <21 vs. 23-26 was associated with dementia . Ns when excluding those that became demented during the first 3 years of follow-up.
Yamada et al., 2003 ¹¹⁴ Adult Health Study, Japan	N=1774, age range 30s to 70s (96 % 30s to 50s)	Population-based study, 25 to 30 years follow-up	Continuous	Age, sex, education	No association between midlife BMI and incident VaD or AD .
Rosengren et al., 2005 ¹¹⁶ Gothenburg, Sweden	N=7402 men, 47-55 years without stroke or MI	Population-based study with registry follow-up during 28 years	BMI < 20, 20-22.5, 22.5-25, 25-27.4, 27.5-30, ≥ 30 kg/m ²	Age, smoking, social class, SBP, diabetes mellitus, cholesterol	BMI < 20, and BMI > 27.5 compared with 20-22.5 was associated with an increased risk of dementia .
Whitmer et al., 2005 ¹¹⁷ California, USA	N=10276, 40-45 years, medicare participants	Population-based study with registry follow-up during 27 years	BMI <18.5, 18.6-24.9, 25-29.9, ≥ 30 kg/m ²	Age, sex, race, education, marital status, hypertension, diabetes, cholesterol, stroke, heart disease, hyperlipidemia	Increased risk of dementia for BMI 25-29.9, and ≥ 30 compared with BMI 18.5-24.9. Ns for BMI <18.5 vs 18.5-24.9

Abbreviations: ns=not significant; PAQUID=Personnes Agées QUID; SD=standard deviation

Alcohol drinking

Globally, alcohol drinking is very common, and the consumption is highest in the Western countries.¹²³ Heavy alcohol drinking over a long time period may lead to dementia, and specific criteria for alcohol related dementia has been defined.¹²⁴ Alcohol drinking has been proposed to be a possible risk factor also for other dementias in addition to alcohol related dementia, though understanding the association has proved to be difficult. The evidence so far is limited but it is suggestive that moderate drinking might reduce the risk of dementia. The earlier cross-sectional studies dividing persons into drinkers and non-drinkers have mostly reported no significant associations between alcohol and dementia.¹²⁵⁻¹²⁹ A pooled analysis of 11 case-control studies showed no association between alcohol drinking and AD at any level of drinking,¹³⁰ and the first prospective population-based studies also found no associations between alcohol and AD.^{131 132}

The first evidence suggesting that moderate alcohol drinking could be protective against the development of dementia came from the PAQUID study in France.¹³³ Since then, a protective effect of mild-to-moderate or regular alcohol drinking for dementia has been indicated in several other prospective population-based studies.¹³⁴⁻¹³⁷ A summary of the major prospective population-based studies investigating the association between alcohol drinking and dementia is shown in table 3. It has been proposed that the association would be especially beneficial for wine and less so for beer.¹³⁷⁻¹³⁹ However, the results from the Rotterdam study and the Cardiovascular Health Study showed no beverage specific differences.^{53 134} The findings from the Canadian Study of Health and Aging suggest that selective mortality might to some extent explain the observed association between moderate alcohol drinking and dementia.¹³⁶ One should keep in mind that some of the recent prospective studies have shown no association between regular or moderate alcohol drinking and dementia or AD.^{140 141} Whether the divergent findings can be explained by the drinking patterns has not yet been extensively investigated. A recent twin study from Finland showed that binge drinking (i.e. drinking large quantities of alcohol in a single session), or passing out due to alcohol drinking in midlife increased the risk of developing dementia later on.¹⁴² In the same study, moderate drinking at midlife showed a non-significant protective effect.

Table 3. The major prospective population-based studies examining the association between alcohol drinking and dementia

<i>Study</i>	<i>Study population</i>	<i>Study design</i>	<i>Alcohol</i>	<i>Covariates</i>	<i>Outcome and results</i>
Hébert et al., 1992 ¹³¹ East-Boston, USA	N=513, 65+ years, home-living, 56 % women	Population-based study with 5 years follow-up	Yes/no, ounces/d (continuous and in three categories)	Age, sex, education, smoking	AD: ns
Yoshitake et al., 1995 ¹³² Hisayama, Japan	N=828, 65+ years, 60 % women	Population-based study with 7 years follow-up	Alcohol drinking (yes/no)	Age, sex, SBP, stroke, diabetes, Hasagava scale, hematocrit	Risk for VaD , not for AD
Orgogozo et al., 1997 ¹³³ PAQUID, France	N=2273, 65+ years, living at home	Population-based study with 3 years follow-up	None (=1 drink/wk or less), mild, moderate (=3-4drinks/d), heavy	Age, sex, education, occupation, MMSE, vascular factors, family status, subjective health, depression, psychotropics	Moderate wine consumption protective for dementia/AD
Hébert et al., 2000 ¹⁴³ CSHA, Canada	N=904, 65+ years, 58 % women	Population-based study with 5 years follow-up	Alcohol (drunk beer/ wine/ spirits at least once/week)	Age, region	VaD: ns
Tyas et al., 2001 ¹⁴⁰ Manitoba, Canada	N=694, 65+ years, 62 % women	Population-based study with 5 years follow-up	Regular drinker, beer, wine, spirits (at least once/wk)	Age, sex, education	AD: ns
Huang et al., 2002 ¹³⁵ KP, Sweden	N=402, 75+ years, 82 % women	Population-based study with 6 years follow-up	None vs. moderate (1-14 units/wk women, 1-21 men)	Age, sex, education, MMSE, smoking, institutionalisation	Light to moderate drinking had protective effect for dementia and AD
Lindsay et al., 2002 ¹³⁶ CSHA, Canada	N=4688, 65+ years, non-institutionalised, 58 % women	Population-based study with 5 years follow-up	Regular drinker, beer, wine, spirits (=at least once/wk)	Age, sex, education	AD: Regular alcohol and wine consumption protective, but beer and spirits consumption are not. Ns when estimation of the decedents in the analyses
Ruitenberget al., 2002 ¹³⁴ Rotterdam, Holland	N=5395, 55+ years, 59 % women	Population-based study with 6 years follow-up	No, <1 drink/wk, 1-7/wk, 1-3/d, 4+/d	Age, sex, BMI, SBP, diabetes, smoking, education	Moderate drinking (1-3/day) associated with lower risk of dementia and VaD . Similarly for AD among ApoE4+. No beverage differences

Table 3. The major prospective population-based studies examining the association between alcohol drinking and dementia (**cont.**)

<i>Study</i>	<i>Study population</i>	<i>Study design</i>	<i>Alcohol</i>	<i>Covariates</i>	<i>Outcome and results</i>
Truelsen et al., 2002 ¹³⁸ CCHS, Denmark	N=1709, 65+ years, 62 % women	Population-based study with 15 years follow-up	1. Weekly drinking (units); 2. Never, monthly, weekly, daily beer, wine and spirits	Age, sex, education, stroke, cohabitation, income, SBP, smoking, other alcohol types	Average drinking (units/week) ns. Monthly/weekly wine intake associated with decreased risk, monthly beer intake with increased risk of dementia
Mukamal et al., 2003 ⁵³ CHS, USA	Cases=373, controls=373 65+, years	Nested case-control study, with 6 years follow-up	Drinks/week: <1, 1-6, 7-13, 14+	Age, sex, race, ApoE4, education, income, marital status, ERT, smoking, DM, BMI, cholesterol, AF, heart failure, TIA, stroke, energy	U-shape for dementia, and AD , tendency for VaD . No beverage differences. Trend for increased risk with heavier drinking among ApoE4 carriers
Luchsinger et al., 2004 ¹³⁹ New York, USA	N=980, 65+ years, 67 % women	Population-based study with 4 years follow-up	None, moderate (<3 servings/d), heavy drinkers	Age, sex, ApoE4, education, other alcohol	Moderate wine associated with a lower AD risk. Other alcohol ns. Ns with additional adjustments. Ns for dementia with stroke
Deng et al., 2005 ¹³⁷ Chongqing, China	N=2632, 60+ years, 56 % women	Population-based study with 2 years follow-up	<1 unit/wk, 1-14, >14 (women); <1, 1-21, >21 (men)	Age, sex, education, blood pressure, smoking, stroke, MMSE	Moderate drinkers had lower risk of dementia, AD and VaD . Moderate beer increased, and wine decreased dementia risk
Järvenpää et al., 2005 ¹⁴² Twin cohort, Finland	N=554 twins, 65+ at follow-up	Population-based twin study with 25 years follow-up	0, <3, 3-7, 7+ units/wk (women); 3-14, 14+ (men). Binge drinking, and alcohol passouts	Age, sex, education, drinking patterns	Any level of alcohol units/week was not associated with dementia. Midlife monthly binge drinking and passing out increased the dementia risk.
Simons et al., 2006 ¹⁴⁴ Dubbo study, Australia	N=2805, 60+ years, 56 % women, non-institutionalised	Population-based study with 16 years follow-up, registry dg	Any versus none	Age, marital status, education, stroke, ADL, gardening, walking, PEF, depression	Alcohol drinking was associated with decreased risk of hospital admission due to dementia
Yip et al., 2006 ¹⁴¹ MRC-CFAS, UK	N=4075, 65+ years, 63 % women	Population-based study with 6 years follow-up	1. Never, past, current 2. none, normal, excessive	Age, sex, education, social class	Dementia : ns

Abbreviations: ADL=activities of daily living; AF=atrial fibrillation; CCHS=Copenhagen City Heart Study; CHS=Cardiovascular Health Study; CSHA=Canadian Study of Health and Aging; d=day; DM=diabetes mellitus; ERT=estrogen replacement therapy; KP=Kungsholmen Project; MRC-CFAS=Medical Research Council Cognitive Function and Ageing Study; PAQUID=Personnes Agées QUID; PEF=peak expiratory flow; TIA=transient ischemic attack; wk=week

With regards to excessive alcohol drinking, it has been shown that a history of heavy drinking or alcohol abuse might be associated with an increased occurrence of dementia and AD,¹⁴⁵⁻¹⁴⁹ but other studies have detected no association between alcohol problems, alcohol abuse or heavy alcohol intake and AD.¹⁵⁰⁻¹⁵³

The long-term effects of alcohol drinking for cognitive functions have been studied with varying results. Some studies have used the results of the cognitive tests as a substitute for a dementia diagnosis, while others have aimed at evaluating the role of alcohol on the level of cognitive performance in the non-demented population. The major prospective studies investigating the association between alcohol drinking and cognitive functions are listed in table 4. The few prospective studies that have assessed changes in cognition prospectively have generally had very short follow-up times, from 1 to 4 years. Two of these studies found no association between alcohol drinking and impairment in global cognitive function,^{154 155} but one study did indicate that increased alcohol drinking was associated with a decrease in global cognitive function.¹⁵⁶ Among the participants (all female) of the hormone therapy trial, Women's Health Initiative Memory Study, and the Nurse's Health Study, moderate alcohol drinking was associated with a decreased risk of decline in global cognitive function.^{157 158} The Eugeira study found that drinkers exhibited a greater decrease in attention, but no associations were seen for memory, visuospatial or language measures.¹⁵⁹ Alcohol drinking was not associated with immediate memory or orientation in the East Boston study, but moderate drinking was associated with less decline in psychomotor speed compared with non-drinking.¹⁶⁰ The Monongahela Valley Independent Elders Survey project which had a seven years follow-up, found that minimal-to-moderate drinking was associated with less decline in global cognitive function, psychomotor speed and executive function, but did not detect any associations between alcohol drinking and visuospatial, memory or fluency measures.¹⁶¹

Table 4. The major *prospective* studies examining the association between alcohol drinking and cognitive functions

Study	Study population	Study design	Alcohol	Covariates	Outcome and results
Hébert et al., 1993 ¹⁶⁰ East Boston, Massachusetts, USA	N=1201, 65+ years home-living men (38 %) and women (62 %)	Population-based study with 3 years follow-up.	none, <0.5 oz/d, 0.5-1 oz/d, ≥1 oz/d, and as continuous.	Age, sex, education, and income	Digit span normal score change in 3 years was better in 0-0.5 oz/d compared to nondrinkers; ≥1 oz/d ns. No association with immediate memory and test of orientation.
Launer et al., 1996 ¹⁵⁵ Zutphen study, Netherlands	N=333 (n=489 for cross-sectional analyses), 65-84 years old men	Population-based study with 3 years follow-up.	none, < 1 drink/d, 1-2, ≥3 drinks/d.	Age, education, and smoking	No association between alcohol and cognitive decline (difference in MMSE between two time points).
Leibovici et al., 1999 ¹⁵⁹ Eugeria study, Southern France	N=225, 60+ years, men and women, below maximal DECO scores at baseline	A GP-based prospective study with 3 annual visits	Information collected at last visit : non-drinkers and drinkers (≥ ¼ litre/d) of wine.	Age, sex, and education	Drinkers had better performance on attention during second year, but they showed higher drop during the following year. No differences were seen in primary, secondary, and implicit memory, visuospatial ability or language.
Cervilla et al., 2000 ¹⁵⁴ Gospel Oak, London, UK.	N=451, 65+ years old cognitively intact at baseline	Population-based study with 1-year follow-up.	0, 1-10, 11-30, >30 units/wk, before age 65, after 65, week before baseline.	Age, sex, smoking, occupation, education, handicap, depression and baseline cognitive function	Incident cognitive impairment (OBS>4) was not associated with alcohol drinking.
Dufouil et al., 2000 ¹⁵⁶ EVA study, Nantes, France	N=1389, 59-71 years at baseline, men (41%) and women (59 %)	Population-based study with 4 years follow-up.	Daily consumption divided into: never, <2, 2-5, ≥5 drinks/d	Age, sex, education, cognitive functions, hypertension, and depressive symptoms	Risk of cognitive deterioration (drop of 3 points or more in MMSE) was increased with alcohol among ApoE4+, tendency for risk decrease with alcohol among ApoE4-.
Leroi et al., 2002 ¹⁶² Epidemiologic Catchment Area Study, Baltimore, USA	N=1488, 18+ years old (18 % aged 61+) men (37 %) and women (63 %)	Population-based study with examinations in 1981, 1982, and 1993.	At any examination: none, social, habitual, heavy infrequent, and heavy frequent users. Dg of alcohol abuse.	Age, race, and education	No significant differences in association between alcohol drinking and decline in MMSE score between 1982 and 1993.

Table 4. The *prospective* studies examining the association between alcohol drinking and cognitive functions (**cont.**)

Study	Study population	Study design	Alcohol	Covariates	Outcome and results
Espland et al., 2005 ¹⁵⁷ WHIMS, USA	N=4461, 65-79 years, female participants in a hormone therapy trial	Prospective study with 4.2 years follow-up.	Alcohol intake over 3 months divided into none, <1 drink/d, ≥1 drink/d	Age, menopause, race, education, income, smoking, BMI, CVD, hypertension, DM, statin, aspirin, hormone use.	Baseline 3MS score increased with drinking. Risk of decline of 8 points or more in 3MS : Non drinker 1(ref.) <1 drink/d 0.69 (0.49-0.97) ≥1 drink/d 0.53 (0.28-0.99)
Ganguli et al., 2005 ¹⁶¹ MoVIES project, Pennsylvania, USA	N=1098, 66+ years, 61 % women, home-living, at least 6th grade education	Population-based study with 7 years follow-up	Drinking trajectories assessed every two years: none, minimal (<once per month), moderate drinking	Age, sex, education, depression, smoking, MMSE, baseline cognition, dementia onset	Minimal and moderate drinkers vs. nondrinkers (or quitters) had less decline in MMSE and trailmaking, minimal drinkers in learning and naming. Ns for memory, visuospatial, and fluency.
Stampfer et al., 2005 ¹⁵⁸ Nurses' Health Study, USA	N=11102, 70+ years, registered nurses, excluding institutionalised, stroke, change in alcohol intake, drank >30 g/d, antidepressants	Prospective study with two telephone cognitive assessments with 1.8 years interval.	Alcohol consumption during previous year from most recent questionnaire prior to first cognitive assessment divided into nondrinkers, 1-14.9g/d, and 15-30 g/d	Age, education, BMI, hypertension, cholesterol, DM, CVD, physical activity, smoking, menopause, hormone therapy, vitamin E supplement, aspirin and ibuprofen use, mental health, energy-fatigue index, baseline cognition	Women drinking 1-14.9 g/d had OR for decline for TICS score 0.85 (0.74-0.98), and OR for declined verbal memory score (lowest 10 %) 0.83 (0.72-0.97), and OR for decline in global cognitive score (lowest 10 %) 0.89 (0.77-1.03). Those drinking 15-30 g/d did not differ from nondrinkers.

Abbreviations: CVD=cardiovascular disease; d=day; DECO=Détérioration Cognitive Observée, an instrument based on a degree of change in behaviour over the last year estimated by a proxy; DM=diabetes mellitus; g=gram; GP=general practitioner; ns=not significant; OBS= organic brain syndrome scale containing 10 items: doesn't know his/her age, year of birth, number of years living in neighbourhood, his/her address, rater's name on first and second try, can't recall Prime Minister's name, doesn't know month, year, failed knee-hand-ear test; oz=ounce; TICS-m=10 minute telephone interview modified from MMSE; 3MS=modified MMSE; MoVIES=Monongahela Valley Independent Elders Survey; WHIMS=Women's Health Initiative Memory Study; wk=week

Four studies have investigated the associations between current cognitive performance and information on alcohol drinking collected 5 to 20 years earlier. The details of these studies are shown in table 5. Both alcoholics and past drinkers had lower global cognitive function compared with non-drinkers or moderate drinkers in a study of male army veterans.¹⁶³ No beverage specific differences were observed in the study. Another small (n=209) veteran study did not find any association between cognitive performance and alcohol drinking.¹⁶⁴ A better global cognitive function among moderate drinkers, and lower among heavy drinkers compared with non-drinkers was found among Japanese-American men.¹⁶⁵ A Dutch population study including both sexes found better psychomotor flexibility and speed among moderate drinkers, but better memory among heavy drinkers than among non-drinkers.¹⁶⁶

In several cross-sectional studies, moderate alcohol drinking compared with non-drinking has been associated with better global cognitive function,¹⁶⁷⁻¹⁶⁹ episodic memory, semantic memory, learning, and abstract thinking.¹⁷⁰ On the other hand, a better performance with increasing levels of alcohol drinking has been observed in several cognitive functions.¹⁷⁰⁻¹⁷³ However, one study did report daily alcohol drinking to be associated with poorer global cognitive function.¹⁶⁸ Finally, a large number of studies have found no associations between alcohol drinking and a wide range of cognitive functions.^{169 171 174 175}

ApoE ϵ 4 has been proposed to modify the effects of alcohol on the risk of developing cognitive impairment^{156 167} or dementia.^{53 134} However, the observed pattern of the effect modification has been different across the studies. A couple of studies have attempted to detect an interaction between smoking and alcohol drinking for the cognitive function and the development of dementia, but have yielded inconclusive results.^{159 174 176}

Table 5. The studies examining the association between current cognitive function and previous alcohol exposure

<i>Study</i>	<i>Sample</i>	<i>Study design</i>	<i>Alcohol</i>	<i>Covariates</i>	<i>Outcome and results</i>
Christian et al., 1995 ¹⁶³ NAS-NRC twin registry, USA.	N=4739, Caucasian male veterans.	Longitudinal study with cognitive assessment in 1990-91 and exposure assessment in 70's and 80's.	Drinks/ wk in 70's and 80's averaged and divided into quintiles, non-drinkers and past drinkers, and alcoholics.	Age and education	Alcoholics performed poorer than others on TICS-m. Past drinkers poorer than non-drinkers, and 2 nd , 3 rd , and 4 th quintile of drinkers. 4 th quintile better than 1 st and 5 th quintile. No beverage specific differences.
Dent et al., 1997 ¹⁶⁴ Sydney, Australia	N=209, WWII male veterans	Longitudinal study with cognitive assessment in 1991 and exposure assessment in 1982.	Quantity-frequency method divided into none, 1-40 g/d, 40-60 g/d, 60-129 g/d	None	No association for any of the 18 tests: WAIS: digit span, block design, similarities; immediate and delayed memory, Benton visual retention, Raven's matrices, Rey auditory verbal learning, controlled oral word association, Boston naming test, National adult reading test, Reaction time, Halstead Reitan battery
Galanis et al., 2000 ¹⁶⁵ Honolulu-Asia Aging Study, USA	N=3556, 71-93 years old Japanese American men	Longitudinal study with cognitive assessment in 1991-1993 and exposure assessment in 1971-74, and at follow-up.	Alcohol continuous and divided into none, 1-2 oz/month, 3-15, 16-30, 31-60, >60 oz/month.	Age, education, migration status, smoking, history of stroke.	The risk of poor CASI (<74) versus good (≥82) was lowest for 3-15 oz/mo 0.60 (0.44-0.82), and highest for > 60 1.29 (0.83-2.01), (0 was ref.). Those who drank 1-15 oz/mo on both occasions had OR 0.34 (0.20-0.60) for poor CASI compared to non-drinkers on both times.
Kalmijn et al., 2002 ¹⁶⁶ MORGEN study, Netherlands	N=1927, 45-70 years old men (48%) and women (52%)	Population-based longitudinal study with exposure assessment 5 years prior to the cognitive assessment.	Alcoholic drinks/ d divided into none, ≤1 drink/d, 1-2, 2-4, 4-8, >8 drinks/d.	Age, sex, education, BMI, cholesterol, SBP, smoking	Those drinking 1-2 and 2-4 drinks/d were better in tasks of psychomotor speed and flexibility compared to non-drinkers. Those drinking >8 drinks/d were better in memory task than non-drinkers. Interaction sex*alcohol for psychomotor speed: for women association was linear and positive.

Abbreviations: CASI=cognitive abilities screening instrument including tests of attention, concentration, short- and long-term memory, language, visual construction, list-generating fluency, abstraction, and judgement; range 0-100; d=day; g=gram; mo=month; MORGEN=Monitoring Project on Cardiovascular Disease Risk Factors; NAS-NRC=National Academy of Sciences – National Research Council; oz=ounce; TICS-m=10 minute telephone interview modified from MMSE; WAIS=Wechsler adult intelligence scale; wk=week; WWII=World War II; 3MS=modified MMSE

Education

The association between education and dementia has been extensively studied. The initial evidence for a link emerged from clinical and cross-sectional studies indicating that the prevalence of dementia and AD was increased among those individuals with no or low education.¹⁷⁷⁻¹⁷⁹ However these findings were not uniform across studies.^{127 180} Subsequently low education has been shown to be associated with an increased risk of dementia and AD in a large number of prospective cohort studies,^{136 140 181-190} but some contradictory findings also exist.^{62 132 191-195} The major prospective studies which have investigated the education – dementia association are described in table 6. In addition, the European Studies of Dementia (EURODEM), which is a pooled analysis of four European incidence studies, showed that low education (≤ 7 years) was associated with risk for dementia and AD among all individuals, especially women.¹⁸¹ The Rotterdam study, that was also included in the above pooled analysis, has proposed that the education – dementia association would be especially pronounced in women.¹⁸⁹ The Nurses Health Study, that investigated a population of over 15,000 elderly female nurses, found that in this well-educated population, those that had a higher education (above registered nurse diploma) had higher cognitive performance and less decline over time in several cognitive measures.¹⁹⁶

It has been suggested that differences in the pre-morbid cognitive function would explain at least partly the association between education and dementia. One study showed that the association between education and dementia was diluted by the effect of baseline cognitive function,¹⁸⁷ but in another study the association remained even when baseline cognition was taken into account.¹⁹⁷ The Amsterdam Study of Elderly showed an increased risk of dementia in individuals with low education,¹⁸⁶ but the association disappeared when premorbid intelligence was taken into account.¹⁹⁴ Studies with autopsy data have shown that while education is associated with clinical AD, it is not related to the neuropathological changes.¹⁹⁸⁻²⁰⁰ At the moment there is fairly strong evidence that low education is associated with an increased risk of dementia and AD, but the mechanisms behind this association remain unclear.

Table 6. The major *prospective* studies examining the association between education and dementia

Study	Sample	Study design	Education	Covariates	Outcome and results
Paykel et al., 1994 ¹⁹⁵ Cambridge, UK	N=1195, urban, 75+ years, 66 % women	GP-list based study, 2 years follow-up	Leaving school >14 years of age, ≤14 years	Age	Ns for dementia .
Stern et al., 1994 ¹⁹⁰ New York, USA	N=594, 60+ years, no stroke or Parkinson's, 73 % women	Population from institutions, registries, volunteers, health care agencies, 1-4 years follow-up	<8, ≥8 years	Age, sex, occupation	Risk of dementia increased with low education.
Cobb et al., 1995 ¹⁹² Framingham study, USA	N=3330, 55-88 years, 60 % women	Population-based study 17 years follow-up	<Grade school, <high school, and ≥ high school	Age	Ns for dementia or AD . Low education associated with non-AD dementia , but ns when smoking was added as covariate.
Yoshitake et al., 1995 ¹³² Hisayama, Japan	N=828, 65-98 years, 60 % women	Population-based study, 7 years follow-up	≤ 6, > 6 years	Age	Ns for AD and VaD .
Evans et al., 1997 ¹⁸³ East-Boston, USA	N=642, 65+ years, 56 % women	Population-based study, 4 years follow-up	In years	Age, sex, follow-up time, income, occupation	Low education was associated with increased risk of AD .
Schmand et al., 1997 ¹⁹⁴ AMSTEL, Holland	N=2063, 65-84 years, 63 % women	Population-based study, 4 years follow-up	In years	Age, sex, DART, occupation, family history, diseases	Ns for dementia.
Geerlings et al., 1999 ¹⁸⁶ AMSTEL, Holland	N=3778, 65-84 years, 62 % women	Population-based study, 3 years follow-up	Primary education or less vs. at least partial secondary education	Age, sex	Low education was associated with incident AD .
Letenneur et al., 1999 ¹⁸⁸ PAQUID, France	N=2881, home-living, 65+ years, 58 % women	Population-based study, 5 years follow-up	Low (without primary school diploma), high	Age, sex	Increased risk dementia and AD with low education.

Table 6. The major *prospective* studies examining the association between education and dementia (**cont.**)

Study	Sample	Study design	Education	Covariates	Outcome and results
Ott et al., 1999 ¹⁸⁹ Rotterdam study, Netherlands	N=6827, 55+ years, 60 % women	Population-based study, 2 years follow- up	<7 years, 7-10, ≥11 years	Age	Increased risk of dementia and AD for lowest vs. highest education among women. Ns among men.
Ganguli et al., 2000 ¹⁸⁵ MoVIES, Pennsylvania, USA	N=1298, 65+ years, home- living, ≥ 6 th grade, 55 % women	Population-based study, 9-11 years follow-up	<High school vs. ≥high school education	Age, sex	Low education was associated with increased risk of dementia and AD with CDR ≥ 0.5. Ns for dementia or AD with CDR ≥ 1.
Kawas et al., 2000 ¹⁹³ BLSA, USA	N=1236, home- living, 55+ years, 35 % women	Volunteer cohort, 8 years follow-up	4-12, 13-16, 17-25 years	Age, sex	Ns trend for lower risk of AD with higher education.
Borenstein Graves et al., 2001 ¹⁹¹ King County, WA, USA	N=1869, 65+ years, Japanese Americans, 56 % women	Population-based study, 4 years follow- up	In years	Age, sex, head circumference, ApoE4	No association between education and AD in adjusted analyses. In univariate analysis the AD subjects had lower education.
Gatz et al., 2001 ²⁰¹ Sweden	143 discordant twin pairs, and 221 cases + 442 unrelated controls	Twin-study with prevalence and incidence estimates.	Low (elementary or less), high	Age, sex, familial characteristics	Association between low education and AD , but not dementia prevalence in case-control analyses. No association for incident cases.
Qiu et al., 2001 ¹⁹⁷ Kungsholmen Project, Sweden	N=1296, 75+ years, 76 % women	Population-based study, 3 years follow- up	<8, ≥ 8 years	Age, sex, MMSE vascular disease, occupation	Low education was related to increased incidence of dementia and AD , but not to mortality of subjects with dementia or AD.
Scarmeas et al., 2001 ²⁰² New York, USA	N=1772, 65+ years, 68 % women	Population-based (health organization), 3 years follow-up	<8, ≥8 years	Age, sex, race, leisure activities, occupation	Ns trend for an increased risk of AD for lowest vs. highest education.
Tyas et al., 2001 ¹⁴⁰ MSHA, Canada	N=694, 65+ years, 62 % women	Population-based study, 5 years follow- up	In years	Age, sex	Decreased risk of AD with increasing education.

Table 6. The major *prospective* studies examining the association between education and dementia (**cont.**)

Study	Sample	Study design	Education	Covariates	Outcome and results
Di Carlo et al., 2002 ¹⁸² ILSA study, Italy	N=2498, 65-84 years, 47 % women	Population-based study, 4 years follow-up	0-5 years, 6-10 years, ≥ 11 years	Age, sex	Middle and high (vs. low) education was associated with reduced risk of dementia and AD . Ns tendency for VaD .
Kukull et al., 2002 ¹⁸⁷ ACT study, Seattle, USA	N=2356, home-living, 65+ years, 60 % women	Population-based (health organisation), 5 years follow-up	<12, 12-15, >15 years	Age, sex, ApoE4, race, baseline cognition (CASI)	Low education was associated with decreased risk of dementia and AD . Ns for non-AD dementia. All ns when baseline CASI added.
Lindsay et al., 2002 ¹³⁶ CSHA, Canada	N=4615, home-living, 65+ years, 58 % women	Population-based study, 5 years follow-up	0-8, 9-12, ≥ 13 years	Age, sex,	Increased risk of AD for lowest vs. highest education.
Wilson et al., 2002 ⁶² Religious Orders Study, USA	N=724 catholic clergy, 65+ years, 67 % women	Population of nuns, priests and brothers, 5 years follow-up	In years	Age, sex, cognitive activities	Ns for AD .
Fitzpatrick et al., 2004 ¹⁸⁴ 4 US communities	N=3602, 65+ years, 59 % women	Random sample from Medicare lists, 5 years follow-up	<High school, high school graduates, \geq some college	Age	Among whites, low education was associated with increased risk of dementia . Ns among African Americans.
Karp et al., 2004 ²⁰³ Kungsholmen Project, Sweden	N=931, 75+ years, 77 % women	Population-based study, 3 years follow-up	Low (2-7 years), high (≥ 8 years)	Age, sex, vascular diseases, alcohol SES	Low education was associated with increased risk of AD and dementia .

Abbreviations: ACT=Adult Changes in Thought study; AMSTEL=Amsterdam Study of Elderly; BLSA=Baltimore Longitudinal Study of Aging; CASI=Cognitive Abilities Screening Instrument; CDR=Clinical Dementia Rating; CSHA=Canadian Study of Health and Aging; DART=Dutch Adult Reading Test (measure of intelligence); GP=general practitioner; ILSA=Italian Longitudinal Study of Aging; MoVIES=Monongahela Valley Independent Elders Survey; MSHA=Manitoba Study of Health and Aging; ns=not significant; PAQUID=Personnes Agées QUID; SES=Socioeconomic status

Socioeconomic factors

Apart from education, several other measures of socioeconomic status have been investigated. In this section, the focus will be on the occupation, occupational exposures and income. Much of the information has originated from case-control or cross-sectional studies. Manual work (farming, factory),^{149 180 204} as well as occupational exposure to electromagnetic fields,²⁰⁵⁻²⁰⁷ or solvents²⁰⁸ have been proposed to be associated with an increased risk of dementia, and mentally demanding work with a decreased risk of dementia.²⁰⁴ However, several cross-sectional or case-control studies have detected no association between dementia and occupation,²⁰⁹ occupational exposure to aluminium,²¹⁰ or solvents,²¹¹ or electromagnetic fields.²¹² In one study, low socioeconomic status in childhood was proposed as a risk factor for AD.²¹³ In the same study, the risk was especially prominent among the ApoE ε4 carriers. One study showed that while neither low education nor rural residence in childhood alone increased the risk of AD, the combination of both of these factors was associated with an increased risk of AD.²¹⁴

The prospective studies investigating the association between socioeconomic factors and dementia are listed in table 7. Manual occupation, low lifetime occupational attainment, occupational exposure to electromagnetic fields, and to fumigants have been shown to be associated with an increased risk of dementia.^{140 183 215 216} Other studies have failed to find any association between dementia and occupation,^{195 202 217} or occupational exposure to various chemicals,¹⁴⁰ radiation,¹³⁶ or magnetic fields.²¹⁶ In some of the studies, the associations were attenuated when the effect of education was taken into account.^{183 203} One study revealed that also low income level was associated with an increased risk, but also here the effect was diluted when education was taken into account.¹⁸³ An interaction between education and occupation has also been proposed in one study – those persons with both low education and low-level occupation seemed to be at the greatest risk of suffering dementia.¹⁹⁰ A small German study has proposed that while high occupational status might be associated with a decreased risk of dementia, poor quality housing could be associated with an increased risk of dementia.⁵⁹ Low childhood socioeconomic status was associated with poor cognitive function but not with an increased risk of AD in a cohort of catholic clergy.²¹⁸

Table 7. The major prospective studies examining the association between socioeconomic factors and dementia

<i>Study</i>	<i>Sample</i>	<i>Study design</i>	<i>Socioeconomic factor</i>	<i>Covariates</i>	<i>Outcome and results</i>
Bickel et al., 1994 ⁵⁹ Mannheim, Germany	N=312, 65+ years, 64 % women	Population-based study with 7-8 years follow-up	Occupation, social class, monthly income, accommodation	Age	Poor accommodation associated with higher risk, and professional occupation with lower risk of dementia , especially VaD , but not AD .
Paykel et al., 1994 ¹⁹⁵ Cambridge, UK	N=1195, 75+ years, 66 % women	GP-list based, 2 years follow-up	Social class: manual, non-manual	Age, sex, education	Ns for dementia .
Stern et al., 1994 ¹⁹⁰ New York, USA	N=594, 60+ years, high-risk persons, excluding PD, 73 % women	Population from medical settings, and volunteers, 1-4 years follow-up	Low: unskilled, skilled trade/craft, clerical; high: manager, professional; housewives	Age, sex, smoking, hypertension, diabetes	Risk of dementia increased with low occupation. Interaction between occupation and education; highest risk with low education and low occupation.
Evans et al., 1997 ¹⁸³ East-Boston, USA	N=642, 65+ years, 56 % women	Population-based study with 4 years follow-up	Annual household income, occupation (perceived prestige).	Age, sex, education, follow- up time	Lower education, income, and occupation each predicted AD incidence. When all 3 measures were included, only education was significant.
Helmer et al. 2001 ²¹⁷ PAQUID, France	N=2950, 65+ years, 58 % women	Population-based study with 10 years follow-up	Professionals, farmers, housewives, blue collar, craftsmen, domestic service	Age, sex, income, education, vascular factors, tobacco, wine	Ns for dementia , AD or VaD .
Scarmeas et al., 2001 ²⁰² New York, USA	N=1772, 65+ years, 68 % women	Population-based study, 3 years follow- up	Low: unskilled, skilled trade/craft, clerical; high: manager, professional; housewives	Age, sex, race, education, leisure activities	Ns for AD .
Tyas et al., 2001 ¹⁴⁰ MSHA, Canada	N=694, 65+ years, 62 % women	Population-based, 5 years follow-up	Occupational exposure to inks, paints, solvents, glues, fuels, fumigants, pesticides, radiation, rubbers, noise, vibration	Age, sex, education	Increased risk of AD with exposure to fumigants, decreased risk with exposure to excessive noise.

Table 7. The major prospective studies examining the association between socioeconomic factors and dementia (cont.)

<i>Study</i>	<i>Sample</i>	<i>Study design</i>	<i>Socioeconomic factor</i>	<i>Covariates</i>	<i>Outcome and results</i>
Lindsay et al., 2002 ¹³⁶ CSHA, Canada	N=4615, 65+ years, 58 % women	Population-based study with 5 years follow-up	Occupational exposure to inks, paints, solvents, rubbers, pesticides, glues, fumigants, radiation, anaesthetics	Age, sex, education	Ns for AD .
Qiu et al., 2003 ²¹⁵ Kungsholmen Project, Sweden	N=913, 75+ years, 76 % women	Population-based study with 6 years follow-up	Non-manual vs. manual work, divided into goods and service production	Age, sex, education, vascular disease	Working with goods production increased the risk of AD , ns trend for dementia .
Karp et al., 2004 ²⁰³ Kungsholmen Project, Sweden	N=931, 75+ years, 77 % women	Population-based, 3 years follow-up	SES: blue collar, white collar/ self-employed/ academic	Age, education, sex, alcohol, vascular diseases	Lower SES associated with increased AD risk. Ns when education was added. Similar findings for dementia .
Qiu et al. 2004 ²¹⁶ Kungsholmen Project, Sweden	N=931, 75+ years, 82 % women	Population-based study with 6 years follow-up	Occupational exposure to ELF-MF ≥ 0.2 microtesla	Age, sex, ApoE, education, mental and social activity, alcohol, smoking, vascular disease	ELF-MF exposure increased risk of dementia and AD and dementia among men. Ns among women.
Wilson et al., 2005 ²¹⁸ Religious Orders Study, USA	N=859 catholic clergy, 65+ years, 69 % women	Population of nuns, priests and brothers, 10 years follow-up	Early life socioeconomic status (socioeconomic features of parents and birth county)	Age, sex, education	Ns for AD .

Abbreviations: CSHA=Canadian Study of Health and Aging; ELF-MF=extremely-low-frequency magnetic field; GP=general practitioner; MSHA=Manitoba Study of Health and Aging; ns=not significant; PAQUID=Personnes Agées QUID; PD=Parkinson's disease; SES=socioeconomic status

Lifestyles and dementia – current status

Lifestyle-related risk factors for dementia have been an area of intensive research in the past few years. At the moment, there is fairly good evidence, that vascular risk factors, including hypertension and hypercholesterolemia, are important in the development of dementia and AD. With regards to obesity, the data is suggestive, but the evidence is not totally convincing. Additionally, it is unclear what the role of obesity is in combination with other vascular risk factors for the development of dementia and AD. Moderate alcohol drinking has been proposed as a protective factor in several longitudinal studies, but contradictory findings also exist. There is no clear picture of what might be the beneficial effect of drinking (if any), and whether the association between alcohol and dementia is similar in different cultural environments. Studies on the socioeconomic status have led to conflicting results perhaps due to the different measures of exposure. Most studies have investigated the role of various occupational categories or occupational exposures to different substances, but less attention has been paid to other socioeconomic factors, such as income. The association between low education and dementia is supported by the majority of studies, but very few studies have investigated whether this association can be attributed to lifestyle factors that covary with education.

AIMS AND HYPOTHESES

The present thesis project aimed at obtaining a comprehensive understanding of the influence of lifestyle-related factors and ApoE genotype in cognitive impairment and dementia. Special attention was paid to possible interactions between environmental and genetic risk factors. The set of studies has been conducted within a large population-based sample of individuals who had been followed on average over a period of 21 years. This provided a unique opportunity to examine the relations between midlife risk factors and the late-life cognitive outcomes. Our general hypothesis was that healthy lifestyle-related factors (e.g. normal body weight, no/little alcohol) might reduce the risk of dementia. More specifically, the study aimed to investigate the following questions:

1. Is midlife BMI related to the risk of dementia and AD later in life? What is the effect of clustering of different vascular risk factors (high BMI, systolic and diastolic hypertension, hypercholesterolemia, smoking) for the risk of dementia? (Study I)
2. Is midlife alcohol drinking related to the risk of dementia and MCI later in life? (Study II)
3. Is alcohol drinking related to different domains of cognitive function among the non-demented? (Study III)
4. Are socioeconomic factors, including education, occupation, and income related to the development of dementia? (Study IV)
5. Can lifestyle-related and vascular factors explain the possible association between education and dementia? (Study V)

The possible effect modification by ApoE ϵ 4 and sex was taken into account in all the studies.

METHODS

Study Population

The participants of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study were derived from population-based independent random samples that were first studied in 1972, 1977, 1982 or 1987 within the framework of the North Karelia Project and the Finnish part of Monitoring Trends and Determinants in Cardiovascular Disease (FINMONICA) study.²¹⁹⁻²²¹ These two studies were conducted to evaluate the risk factors, morbidity, and mortality from cardiovascular diseases. In 1972 and 1977, a random sample of 6.6 percent of the population born in 1913-1947 and living in Kuopio and North Karelia provinces in Eastern Finland 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 10-year age group. This procedure was used to comply with the international WHO MONICA project protocol.²²² The participation rates in these baseline surveys were high, ranging from 83 % to 93 %.²²¹

A random sample of 2000 individuals was invited for the re-examination conducted within the CAIDE study.⁴⁰ Those eligible were aged from 65 to 79 years in 1997, who were still alive and living in or close to the towns of Kuopio and Joensuu. Altogether 1449 (72.5 %) persons participated in the first phase of the re-examination in 1998. The study was approved by the local ethics committees, and written informed consent was obtained from all participants in 1998.

Midlife Examination

The survey methods used during the baseline (midlife) visit were carefully standardized to comply with international recommendations.²²² They also followed the WHO MONICA protocol in 1982 and 1987, and were comparable with methods used in 1972 and 1977.²²¹ In brief, the survey included a self-administered questionnaire on health behavior, health status and medical history. Cerebrovascular and cardiovascular events and conditions diagnosed by a physician were inquired. The questionnaire was mailed to the participants prior to their visit. Nurses specially trained for the survey checked the questionnaires to ensure that they were fully completed. A venous blood specimen was taken to determine serum cholesterol. All

cholesterol determinations were made in the same central laboratory and the laboratory data were standardized against national and international reference laboratories. Systolic and diastolic blood pressures were measured from the right arm of the subjects after they had been seated for five minutes. The weight and height were measured, and BMI was calculated as weight in kilograms divided by the square of height in meters.

Latelife Examination

During the re-examination in 1998, the survey methods followed the previous surveys. Additionally questions related to drug use as well as a questionnaire incorporating questions related to, for example subjective memory, and depressive symptoms were asked of the participants. Further, the participants' ApoE genotypes were determined from blood leukocytes using the polymerase chain reaction and *HhaI* digestion as described previously by Tsukamoto and colleagues²²³ with slight modifications.²²⁴ For the analyses the data of ApoE status were dichotomized: Those with either one or two ApoE ϵ 4 alleles formed one group with the others forming the non-ApoE ϵ 4 group.

Cognitive status was assessed using a three-phase protocol (**figure 1**). In phase 1 (screening phase) all subjects went through a neuropsychological test battery. Those subjects scoring 24 or less on the Mini-Mental State Examination (MMSE)²²⁵ at the screening phase were candidates for phase 2. In the phase 2 (clinical phase) the individuals were subjected to a thorough cardiovascular and neurological examination by a physician, and a detailed neuropsychological evaluation conducted by a neuropsychologist. A review board consisting of the physician, the neurologist, and a senior neurologist ascertained the preliminary diagnoses based on all available information. Those subjects that were judged to have possible dementia at the clinical phase were invited to attend phase 3 (differential diagnostic phase) examination. Phase 3 included brain magnetic resonance imaging (MRI), blood tests, chest radiograph, electrocardiogram, and cerebrospinal fluid analysis. All data accumulated were carefully re-analysed by the review board before establishing the final diagnosis. Phase 1 was conducted at the Department of Public Health and General Practice in the University of Kuopio, and the North Karelia Project Office in Joensuu. Phases 2 and 3 were conducted at the Memory Research Clinic at the Department of Neurology of the University of Kuopio, and the North Karelia Central Hospital in Joensuu.

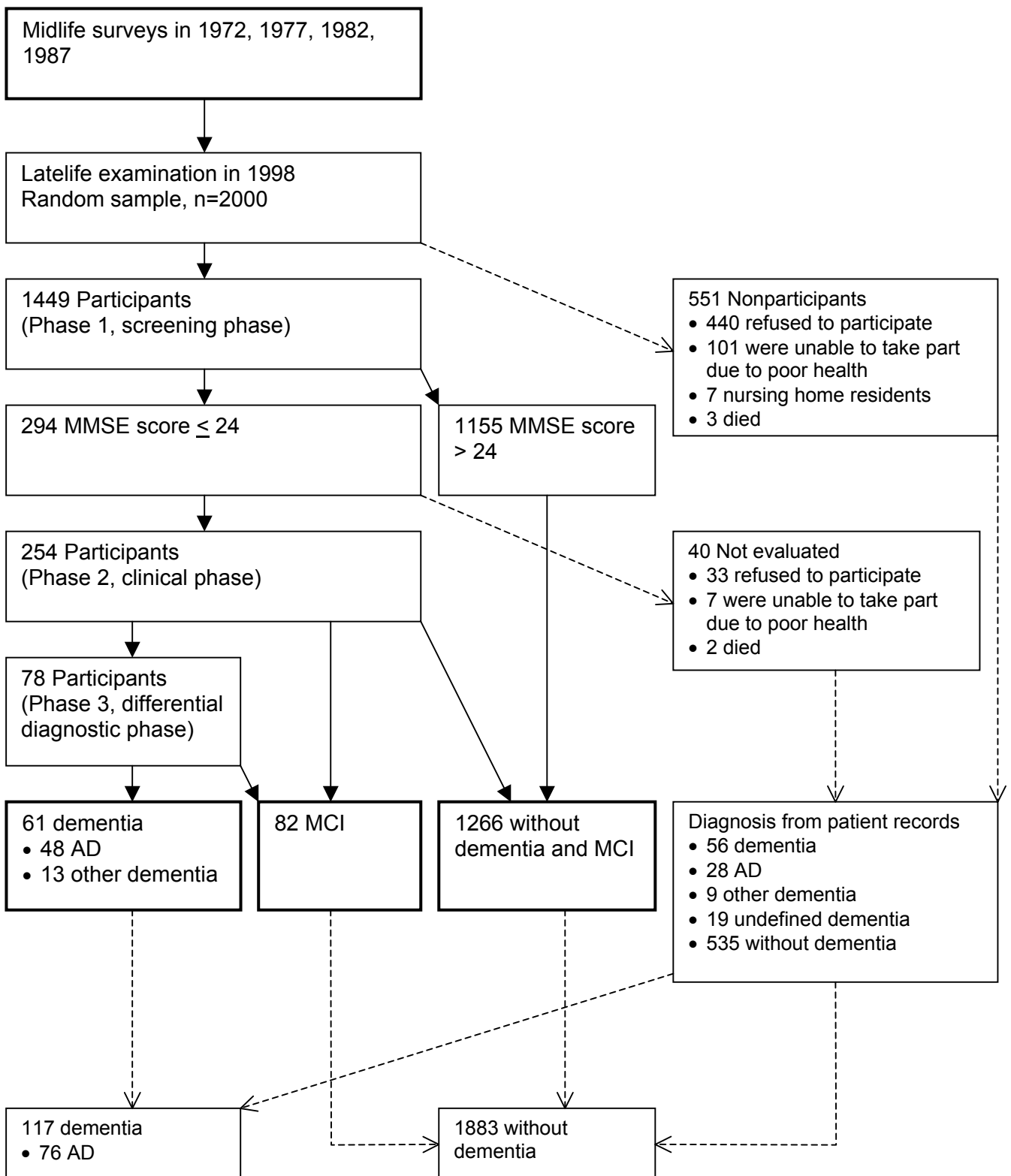


Figure 1. Formation of study population

Diagnostic Criteria

The diagnosis of dementia was based on DSM-IV criteria¹ and the probable and possible AD were diagnosed according to NINCDS-ADRDA criteria.¹⁶ The AD patients displayed generalised and/or medial temporal lobe atrophy, and none had significant vascular pathology on 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 Haschinski Ischemia Scale.²²⁶ The diagnosis of VaD was based on the National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria.²² For other dementia subtypes, the diagnostic criteria used were: consensus diagnostic criteria for frontotemporal dementia,²²⁷ consortium for dementia with Lewy bodies,²²⁸ and consensus criteria for alcohol related dementia.¹²⁴ The dementia diagnoses of the non-participants were derived from patient records of the local hospitals and primary health care centers. There were no records available for 24 of the 551 nonparticipants.

A modification of the Mayo Clinic AD Research Center criteria was used for diagnosing MCI.^{32 33} 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 one other area of cognitive function 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.

Measurement of Cognitive Functions

All participants were subjected to a battery of cognitive tests assessing several cognitive functions in the late-life examination in 1998. The cognitive functions examined included the following:

- MMSE²²⁵ was administered as a measure of global cognitive function.
- Episodic memory was assessed with a test of immediate word recall.^{229 230} The mean number of correct words in three different word lists of 10 words was calculated.
- Semantic memory was assessed with the category fluency test.²³¹ The score was the number of correct animal names generated in 60 seconds.

- Psychomotor speed was analyzed using the sum of the normalized scores in bimanual Purdue Peg Board test²³² and letter digit substitution test.²³³
- Executive function was defined as the difference in the time used in Stroop trial of naming the color of the ink used to write the name of another color, and Stroop trial of naming colors of dots.²³⁴
- In the prospective memory task,²³⁵ at the beginning of the test-session, the subject was asked to remind the investigator, that he/she must sign a paper at the end of the test session. The score in the test was categorized as remembering without reminder (score=4), remembering with one reminder (3), remembering with two reminders (2) or not remembering (1).
- Subjective memory was defined as a mean result of 22 questions²³⁶ all ranging from 1 to 4 with 4 being the lowest subjective memory.

Statistical Methods

The differences between demented and non-demented, as well as between non-participants and participants of the follow-up study were investigated with t test and chi square test. Differences in socioeconomic, lifestyle, and clinical characteristics of the participants according to BMI level (study I), alcohol drinking level (studies II and III), and education level (study V) were assessed with analysis of variance (ANOVA). Multiple logistic regression analyses with adjustments for main confounders were used to calculate odds ratios (OR) with 95 % confidence intervals (95 % CI) for dementia (studies I, II, IV, V), AD (studies I, V), and MCI (study II). In the main analyses, we used only dementia and AD diagnoses from the study to ensure diagnostic accuracy, but we reran the analyses also including dementia cases among the follow-up non-participants from the medical records. Analyses of covariance (ANCOVA) with Bonferroni adjustments for multiple comparisons were used to analyse differences in cognitive test results according to the alcohol drinking frequency (study III). The effect modification by ApoE4 (studies I-V), sex (studies I-V), or smoking (study III) was investigated first by including interaction terms into the analyses, and then carrying out analyses stratified by ApoE ε4/sex/ smoking. We also investigated the odds of dementia in each effect modifier*exposure subgroup by creating variables including all possible groupings. The participants with missing information for one or several of the covariates were excluded from the respective analyses. The level of significance was $p < 0.05$ in all analyses. All analyses were conducted with SPSS for Windows.

Methodological Issues of the Substudies

Study I

In the first study we investigated the association between midlife BMI and dementia/ AD. Also the effect of clustering of vascular risk factors for the risk of dementia was examined. BMI was categorised into three groups using widely recognised cut-off points:¹⁰³ BMI \leq 25 kg/m² (normal weight), BMI 25-30 kg/m² (overweight), and BMI $>$ 30 kg/m² (obesity). The normal weight group was used as the reference category. We conducted the first analyses by adjusting for age, sex, education, community of residence (Kuopio or Joensuu) and follow-up time, and then adjusting further for midlife vascular risk factors including SBP, DBP, serum total cholesterol, and smoking. Finally, we conducted analyses adjusting also for ApoE ϵ 4 status, and history of myocardial infarction, stroke, and diabetes mellitus (inquired at the re-examination). To analyse the effect of clustering of vascular risk factors for dementia and AD, we created binary variables of midlife vascular risk factors (BMI $>$ 30 kg/m², SBP $>$ 140 mmHg, DBP $>$ 95 mmHg, total cholesterol $>$ 6.5 mmol/L, and smoking (yes/ no)). The association between each of these factors and dementia was first investigated in a logistic regression model adjusted with age, sex, education, community of residence, and follow-up time. Second, risk factors that were significantly related to dementia (BMI, SBP, cholesterol) were put into the same model simultaneously to evaluate the independent effect of each risk factor. Third, a summary variable was composed of these binary variables (presence/ absence of high BMI, SBP, and cholesterol) to analyse how an increase in the number of risk factors would be associated with dementia/ AD.

Study II

In the second study we examined the role of midlife alcohol drinking on the subsequent development of dementia and MCI. The analyses were restricted to those participants that were first included in 1972 or 1977, since the information about the frequency of overall alcohol drinking was available only for them. For the analyses, we classified people into three groups: those who never drank alcohol (referred to as “never”), those who drank less frequently than once per month (“infrequent”) and those who drank several times per month (“frequent”). The group of never-drinkers or infrequent drinkers was treated as the reference group depending on the analyses. All analyses were adjusted for age, sex, education, community of residence, and follow-up time. Further analyses controlled also for the variables related with midlife alcohol drinking frequency: midlife BMI, total cholesterol level,

smoking status (smoker/ non-smoker), and for other vascular factors: midlife SBP, history of myocardial infarction, stroke, and diabetes mellitus at the follow-up.

Study III

The third study focused on the association between alcohol drinking and cognitive functioning among those who were non-demented at the time of follow-up. The questions concerning alcohol drinking varied somewhat between different baseline sampling years. In the 1972 and 1977 questionnaires (n=966), the frequency of overall alcohol drinking was determined, and persons were divided into three groups as in study II. Furthermore, the effect of a change in drinking between midlife and late-life was analyzed by grouping persons into a total of nine possible classes, i.e. never-drinker in midlife and never-drinker in late-life etc. In the 1982 and 1987 questionnaires (n=369) the weekly consumption of beer, wine, spirits and so-called long drinks was inquired. This information was used to determine the effect of specific beverages. Furthermore, the total weekly alcohol intake (grams/week) was defined. The variables were divided into three (non-drinkers, drinkers divided into two groups from the median) to allow for non-linear effects. In the calculations, the following alcohol contents were used: a bottle of beer contains 12.5 grams of alcohol, a glass of wine 12 grams, a drink of spirits 12 grams, and a long drink contains 14.5 grams of alcohol. In the follow-up examination in 1998, the questions were comparable to those asked in the baseline years: the alcohol drinking was inquired both as the overall alcohol drinking frequency, and as the amount of beer, wine and spirits, but also of cider/ light wine (alcohol content 6 grams) consumed during the previous week. Also, one question allowed for identification of those individuals who had quit drinking any time prior to the 1998 examination. The analyses were first adjusted for age, sex, education, and follow-up time, and additionally adjustments were made also for midlife SBP, BMI, total cholesterol level, smoking status (smoker/ non-smoker), ApoE ϵ 4 carrier status (ϵ 4 carrier/ non-carrier), history of myocardial infarction, stroke and diabetes (inquired in late-life examination), and living status (alone/ with partner), income level (lower/higher) and depressive symptoms (Beck depression scale²³⁷) in late-life.

Study IV

The fourth study examined the association between dementia and socioeconomic factors, including education, occupation and income. Education was inquired as years of formal education. The original nine income categories were grouped into two categories of lower and higher income, which included approximately the same number of subjects. The change of

income during the follow-up period was stratified into three groups: decreasing, no change and increasing income level. It was defined as a change of the subject from one of the two income categories into another one between the midlife survey and the late-life survey. The subjects reported the occupation they had held for the longest period in their lives (main occupation during life) using predetermined alternatives at the baseline questionnaire. These were grouped into three categories: 1) Farming, animal husbandry, cooking, factory or construction work and mining formed one group and were defined as physical occupations; 2) Office work, intellectual work, and service branch work formed the group of sedentary occupations; 3) Students, housewives, pensioners and the unemployed formed the group of those with no occupation. The associations between dementia and socioeconomic factors were investigated with multiple logistic regression analyses, controlling first for age, sex, community and follow-up time (model 1), then also for ApoE ε4 carrier status (model 2). In the final analyses each socioeconomic factor was additionally controlled for other socioeconomic factors.

Study V

The final study focused on the association between education and dementia and AD. Education level was queried at the midlife examination, and it was categorised into three groups: 0 to 5 years of education (low); 6 to 8 years of education (medium); and nine years or more of education (high). Possible confounders were introduced into the analyses in blocks: 1) Age, sex, follow-up time and community of residence were included. In the following models other possible confounders were introduced in addition to those first included. 2) Midlife vascular and lifestyle characteristics were added including SBP, DBP, total cholesterol, obesity, physical activity, and smoking. 3) Late-life diseases and depressive symptoms were added including myocardial infarction, stroke, diabetes mellitus, and Beck depression scale score.²³⁷ In the final model, the variables in model 1 as well as all the variables significant at level $p=0.10$ in the subsequent models were added. To investigate the hypothesis that the association between education and dementia would be due to a diagnostic bias, we performed two kinds of analyses: First, we limited the analyses to those who were screening positive ($MMSE < 25$) and who thus went through the thorough clinical and neuropsychological examinations. Second, we investigated if the association between education and dementia was similar also among the follow-up non-participants (diagnoses derived from registries).

RESULTS

Characteristics of the Sample

Of the 2000 persons invited to the first phase of the re-examination in 1998, altogether 1449 (72.5 %) persons participated (**figure 1**). 294 persons scored below the cut-off point of ≤ 24 at the MMSE screening test, and were invited to take part in the second phase. Forty persons among them did not participate, leaving 1409 participants with detailed information on their cognitive status. A total of 61 (4.3 %) participants met the diagnosis of dementia, out of which 48 had AD. The total number of demented persons increased to 117 (5.9 % of the total sample of 2000 persons) when diagnoses derived from the patient records for the non-participants were taken into account. There were 82 (5.8 %) participants who were diagnosed as having MCI.

The mean age (SD) of the population at the midlife examination was 50.6 (6.0) years, and the mean age at the late-life examination was 71.6 (4.1) years. There were 1250 women (62.5 %) and 750 (37.5 %) men. Half of the population sampled lived in or close to the town of Kuopio and half lived in or close to the town of Joensuu.

Participants and non-participants

The non-participants of the follow-up study were older than the participants (**table 8**). The non-participants were also less educated, had lower income, and lived more often alone at midlife compared with the participants. The non-participants had more often no occupation at all, or a physical occupation whereas the participants more often had a sedentary occupation at the time of the midlife examination. The vascular risk factor profiles at midlife were worse among the non-participants compared with the participants: systolic and diastolic blood pressure, total serum cholesterol level, and BMI were all higher among the non-participants. The proportion of smokers was also somewhat higher among the non-participants. Dementia was more prevalent among the non-participants (diagnoses derived from patient registries) compared with the participants.

Women and men

Among the participants, the women were slightly older than the men at the time of late-life examination (**table 9**). The mean education was higher among men compared with women,

Table 8. Characteristics of the participants and non-participants of the follow-up study. The values are means (standard deviations) unless otherwise stated.

	All n=2000	Participants n=1409	Non-participants n=591	p*
Demographic characteristics				
Age at midlife, years	50.6 (6.0)	50.4 (6.0)	51.2 (5.9)	<0.01
Sex, %				
Women	62.5	62.1	63.5	0.57
Men	37.5	37.9	36.5	
Community, %				
Kuopio	50.0	49.0	52.3	0.19
Joensuu	50.0	51.0	47.7	
Midlife socioeconomic factors				
Education, years	8.3 (3.4)	8.6 (3.5)	7.5 (3.0)	<0.01
Living status, %				
Alone	21.9	19.6	27.3	<0.01
With partner	78.1	80.4	72.7	
Income level, %				
Lower	43.5	40.6	50.6	<0.01
Higher	56.5	59.4	49.4	
Occupation, %				
No occupation	27.8	25.7	32.7	<0.01
Physical	30.1	28.5	33.8	
Sedentary	42.2	45.8	33.5	
Midlife lifestyle factors				
Systolic blood pressure, mmHg	146.0 (20.6)	144.3 (19.8)	150.2 (21.7)	<0.01
Diastolic blood pressure, mmHg	89.9 (11.1)	89.2 (10.9)	91.7 (11.3)	<0.01
Total cholesterol, mmol/l	6.80 (1.24)	6.73 (1.20)	6.98 (1.32)	<0.01
Body mass index, kg/m ²	26.8 (4.0)	26.6 (3.7)	27.2 (4.5)	<0.01
Smokers, %	44.3	43.0	47.5	0.06
Alcohol drinking, %				
Never	31.1	29.5	34.8	0.13
Infrequent	40.4	41.6	37.9	
Frequent	28.5	29.0	27.4	
Physical activity, %				
Active	40.4	40.7	39.5	0.61
Sedentary	59.6	59.3	60.5	
Late-life diseases				
Dementia, %	5.9	4.8	8.3	<0.01

*p-value for difference between participants and non-participants. T test was used for continuous, and chi square test for categorical variables.

and men also more often had a higher income level. Only one out of ten men lived alone, whereas more than a fourth of women lived alone. Physical occupations were more frequent among men, while having no occupation was more common among women. The proportions of smokers and frequent drinkers were higher in men. Men were also more often physically active. SBP, cholesterol and BMI were similar between men and women, but DBP was higher among men. The occurrence of dementia and AD was similar among men and women, as was the occurrence of stroke and diabetes mellitus. However there were twice as many men who

had suffered a myocardial infarction than women. Women had higher scores on the Beck depression scale in late-life compared with men.

Table 9. Characteristics of all participants and separately for men and women. The values are means (standard deviations) unless otherwise stated.

	<i>All</i> n=1409	<i>Women</i> n=875	<i>Men</i> n=534	p*
Demographic characteristics				
Age at baseline, years	50.4 (6.0)	50.5 (6.1)	50.0 (5.8)	0.12
Age at follow-up, years	71.3 (4.0)	71.5 (4.1)	70.9 (3.9)	<0.01
Follow-up time, years	20.9 (4.9)	20.9 (4.9)	20.8 (4.9)	0.71
Community, %				
Kuopio	49.0	47.8	51.1	0.22
Joensuu	51.0	52.2	48.9	
Midlife socioeconomic factors				
Education, years	8.6 (3.5)	8.5 (3.2)	8.9 (3.8)	0.04
Living status, %				
Alone	19.6	27.0	7.5	<0.01
With partner	80.4	73.0	92.5	
Income level, %				
Lower	40.6	45.9	32.1	<0.01
Higher	59.4	54.1	67.9	
Occupation, %				
No occupation	25.7	33.1	13.5	<0.01
Physical	28.5	20.2	41.9	
Sedentary	45.8	46.6	44.6	
Midlife lifestyle factors				
Systolic blood pressure, mmHg	144.3 (19.8)	144.6 (20.7)	143.6 (18.3)	0.36
Diastolic blood pressure, mmHg	89.2 (10.9)	88.5 (10.7)	90.4 (11.2)	<0.01
Total cholesterol, mmol/l	6.73 (1.20)	6.77 (1.25)	6.67 (1.12)	0.10
Body mass index, kg/m ²	26.6 (3.7)	26.6 (4.0)	26.5 (3.1)	0.61
Smokers, %	43.0	22.9	76.0	<0.01
Alcohol drinking, %				
Never	29.5	39.6	13.0	<0.01
Infrequent	41.6	43.4	38.6	
Frequent	29.0	17.1	48.4	
Physical activity, %				
Active	40.7	37.6	45.7	<0.01
Sedentary	59.3	62.4	54.3	
Late-life diseases				
MCI, %	5.9	6.4	5.2	0.36
Dementia, %	4.3	4.0	4.9	0.44
Alzheimer's disease, %	3.4	3.3	3.6	0.79
Myocardial infarction, %	15.0	10.6	22.0	<0.01
Stroke, %	7.2	6.7	8.1	0.35
Diabetes mellitus, %	6.7	5.8	8.1	0.10
Other characteristics				
Apolipoprotein E ε4 carriers, %	35.6	33.9	38.3	0.10
Beck depression scale in late-life	9.7 (6.6)	10.4 (6.7)	8.6 (6.4)	<0.01

*p-value for difference between men and women. T test was used for continuous, and chi square test for categorical variables.

Mild cognitive impairment

The participants that were diagnosed as having MCI were older than those that were cognitively intact at the time of the late-life examination (**table 10**). The persons with MCI had less education, lived more often alone, had a lower income level, and more often had no occupation or a physical occupation compared with the cognitively normal persons. Total serum cholesterol was higher among those with MCI. The proportion of never drinkers and frequent drinkers was higher among those with MCI, while the proportion of infrequent drinkers was higher among the cognitively normal participants.

Dementia

Also the participants that had dementia were older than those that were cognitively intact at the time of the late-life examination (**table 10**). The demented persons had a lower level of education, they lived more often alone, and more often had no occupation or a physical occupation compared with the cognitively normal persons. The values of midlife SBP, DBP, total serum cholesterol, and BMI were higher among those that became demented. The occurrences of both myocardial infarction and stroke were higher among the demented than among those who were cognitively normal, as was the presence of depressive symptoms. There were more ApoE ϵ 4 carriers among the demented than among the cognitively normal persons.

Table 10. Characteristics of the demented, MCI, and normal participants. The values are means (standard deviations) unless otherwise stated.

	Normal n=1266	MCI n=82	Dementia n=61	p ¹	p ²
Demographic characteristics					
Age at baseline, years	50.1 (6.0)	51.7 (5.8)	53.4 (4.8)	0.02	<0.01
Age at follow-up, years	71.0 (3.9)	72.8 (4.1)	74.5 (3.9)	<0.01	<0.01
Follow-up time, years	20.9 (5.0)	21.1 (4.8)	21.1 (4.4)	0.73	0.71
Sex, %				0.36	0.47
	Women	62.0	67.1	57.4	
	Men	38.0	32.9	42.6	
Community, %				0.03	<0.01
	Kuopio	47.4	59.8	68.9	
	Joensuu	52.6	40.2	31.1	
Midlife socioeconomic factors					
Education, years	8.8 (3.5)	6.8 (2.4)	6.7 (2.6)	<0.01	<0.01
Living status, %				<0.01	0.03
	Alone	18.4	30.5	29.5	
	With partner	81.6	69.5	70.5	
Income level, %				0.02	0.56
	Lower	39.7	53.3	43.6	
	Higher	60.3	46.7	56.4	
Occupation, %				<0.01	0.02
	No occupation	24.7	36.6	31.1	
	Physical	27.6	34.1	39.3	
	Sedentary	47.7	29.3	29.5	
Midlife lifestyle factors					
Systolic blood pressure, mmHg	143.4 (19.4)	148.4 (23.2)	155.4 (20.7)	0.06	<0.01
Diastolic blood pressure, mmHg	89.0 (10.8)	90.6 (11.0)	92.3 (12.2)	0.19	0.02
Total cholesterol, mmol/l	6.68 (1.20)	7.19 (1.22)	7.13 (1.03)	<0.01	<0.01
Body mass index, kg/m ²	26.5 (3.7)	27.1 (3.6)	27.9 (3.9)	0.12	<0.01
Smokers, %	43.3	35.4	45.9	0.16	0.69
Alcohol drinking, %				0.02	0.49
	Never	28.7	41.0	29.2	
	Infrequent	43.0	24.6	35.4	
	Frequent	28.3	34.4	35.4	
Physical activity, %				0.29	0.16
	Active	40.8	46.8	31.7	
	Sedentary	59.2	53.2	68.3	
Late-life diseases					
Myocardial infarction, %	13.7	20.3	35.2	0.11	<0.01
Stroke, %	6.5	9.2	21.8	0.35	<0.01
Diabetes mellitus, %	6.3	8.9	11.3	0.37	0.15
Other characteristics					
Apolipoprotein E ε4 carriers, %	34.5	38.8	54.4	0.44	<0.01
Beck depression scale in late-life	9.6 (6.5)	10.2 (7.9)	12.3 (7.5)	0.52	0.02

p¹ is p-value for difference between controls and MCI, p² for difference between controls and dementia. T test was used for continuous, and chi square test for categorical variables.

Obesity and dementia

Obesity (BMI > 30) at midlife was associated with an increased risk of dementia in the analyses adjusted for sociodemographic factors (**table 11**). The association was somewhat modified when further adjustments were made for midlife vascular factors, ApoE ε4 and late-life vascular disorders. Being overweight (BMI 25-30) was not associated with an increased risk of dementia. Point estimates for the association between obesity and AD were slightly lower than those for dementia, and no longer reached statistical significance. When the analyses were rerun including also the information concerning the non-participants (diagnoses derived from patient registries), the results showed again that the persons who were obese at midlife had an increased risk of subsequently developing dementia.

Table 11. Association between midlife body mass index and dementia

	Odds Ratio (95 % CI)		
	Model 1	Model 2	Model 3
Dementia			
Normal weight	1 (ref.)	1	1
Overweight	1.07 (0.54-2.12)	1.00 (0.51-2.01)	0.99 (0.46-2.13)
Obesity	2.43 (1.17-5.06)	2.00 (0.94-4.28)	1.81 (0.75-4.35)
AD			
Normal weight	1 (ref.)	1	1
Overweight	0.98 (0.47-2.06)	0.97 (0.46-2.06)	0.84 (0.37-1.92)
Obesity	1.88 (0.83-4.27)	1.73 (0.74-4.03)	1.62 (0.63-4.13)
Dementia (including diagnoses for non-participants from registries)			
Normal weight	1 (ref.)	1	NA
Overweight	1.04 (0.65-1.68)	1.00 (0.62-1.62)	
Obesity	1.84 (1.08-3.11)	1.71 (0.99-2.95)	

Model 1 adjusted for age, sex, community, education and follow-up time. Model 2 adjusted additionally for midlife SBP, cholesterol, and smoking. Model 3 adjusted additionally for ApoE ε4 and late-life vascular disorders. NA=not applicable

When late-life diabetes was added into model 1, the association between obesity and dementia was somewhat diminished but nevertheless significant (OR 2.15; 95 % CI 1.01-4.61). In the subgroup of non-diabetics participants, the association between obesity and dementia remained virtually unchanged (OR 2.47; 95 % CI 1.09-5.60 in model 1). In the subgroup of diabetics, there were too few persons to permit any meaningful analyses. Further, when analyses were controlled also for midlife physical activity and fat intake (from spreads and milk products), the results remained essentially unchanged (OR for dementia 2.44; 95 % CI 1.16-5.11 for those with obesity vs. normal weight).

Clustering of Vascular Risk Factors and Dementia

Among the persons that were obese at midlife, there were more persons who had high SBP (> 140 mmHg) than among non-obese persons (72 % vs. 53 %, respectively, $p < 0.01$). Similarly high DBP (> 95 mmHg) was more prevalent among the obese (43.6 %) than non-obese persons (25.3 %; $p < 0.01$). Also hypercholesterolemia (total serum cholesterol > 6.5 mmol/l) tended to be more frequent among the obese persons (59.8 %) compared with the non-obese (55.8 %; $p=0.17$). On the contrary, there were more smokers among the non-obese (45.5 %) than among the obese persons (38.8 %; $p=0.02$).

Three of the investigated midlife vascular risk factors (obesity, hypertension, and hypercholesterolemia) were significantly associated with the risk of dementia when modelled together with demographic characteristics. When they were put simultaneously into a logistic regression model, adjusting for sociodemographic factors, each of these parameters independently increased the risk of dementia with odds ratios of similar magnitude (**table 12**).

Table 12. The independent effect of midlife vascular risk factors for dementia

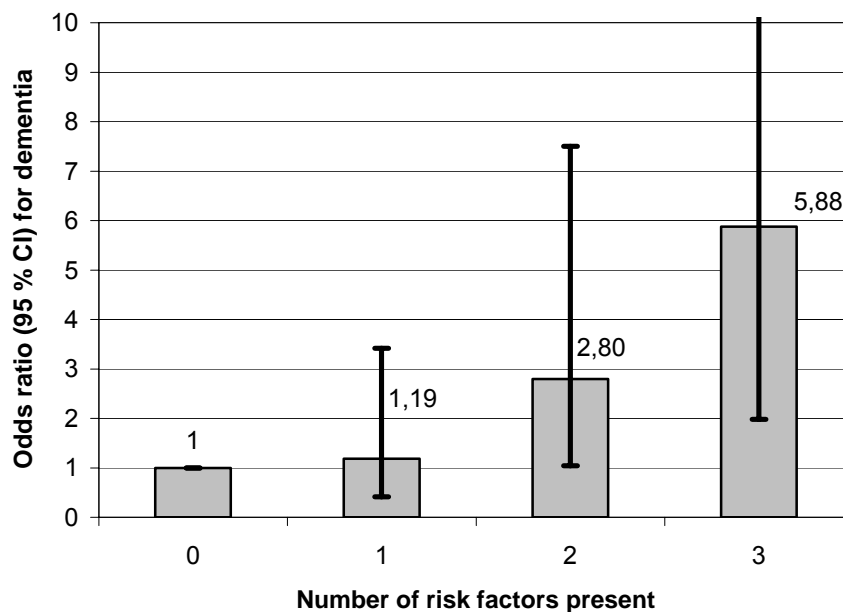
	Odds Ratio (95 % CI) Model 1
Dementia	
Obesity	2.07 (1.14-3.76)
Hypertension	2.04 (1.07-3.87)
Hypercholesterolemia	1.84 (0.99-3.42)
AD	
Obesity	1.78 (0.90-3.52)
Hypertension	1.57 (0.79-3.11)
Hypercholesterolemia	2.10 (1.03-4.28)
Dementia (including diagnoses for non-participants from registries)	
Obesity	1.71 (1.10-2.65)
Hypertension	1.33 (0.87-2.04)
Hypercholesterolemia	1.68 (1.09-2.61)

Model 1 adjusted for age, sex, community, education and follow-up time.

The increasing number of vascular risk factors present at midlife increased the risk of dementia in an additive manner. Compared with persons who had normal weight, normal SBP, and normal serum cholesterol level, those that had all of these risk factors had a more than six-fold increased risk of dementia in the analyses adjusted for sociodemographic characteristics (**figure 2**). Similarly, the risk of AD increased with an increasing number of

risk factors: compared with those with no risk factors, in those with 1 risk factor, the OR (95 % CI) for AD was 1.25 (0.39-4.03); with 2 risk factors it was 2.33 (0.91-8.19); and with all 3 risk factors it rose to 4.54 (1.32-15.59). When repeating the analyses including also the non-participants (diagnoses derived from patient registries), the results were similar showing an increased risk of dementia with increasing number of risk factor present.

Figure 2. Association between number of vascular risk factors present at midlife and the risk of developing dementia.



Risk factor was considered to be present if SBP was > 140 mmHg, or BMI > 30 kg/m² or total serum cholesterol > 6.5 mmol/l. Model 1 adjusted for age, sex, community, education and follow-up time. The black bars represent 95 % confidence intervals.

Alcohol Drinking and Dementia

Information on midlife alcohol drinking frequency was available for the participants who were included in 1972 or 1977. These persons constituted 74 % of the total CAIDE population. Approximately 30 % of the participants did not drink alcohol, 40 % drank infrequently, and 30 % frequently. In the frequent drinkers, about 70 % drank alcohol once or twice per month, 25 % once a week, about 8 % drank a couple of times per week, with one per cent drinking on a daily basis. In the infrequent drinkers, more than 40 % drank alcohol twice a year or less frequently, and about 60 % reported drinking three to six times per year.

The never-drinkers were the oldest in the follow-up examination, and the frequent drinkers were the youngest. The never-drinkers were also less educated, and more women were never-drinkers and infrequent drinkers whereas men were more often frequent drinkers. Smoking was more frequent among frequent alcohol drinkers. BMI and total cholesterol tended to be lower among infrequent drinkers than in the other two groups. The proportion of people with a history of myocardial infarction and stroke did not differ significantly according to the alcohol drinking frequency.

Midlife alcohol drinking frequency was not significantly associated with dementia or AD in the analyses adjusted for sociodemographic factors or after further adjustments (**table 13**).

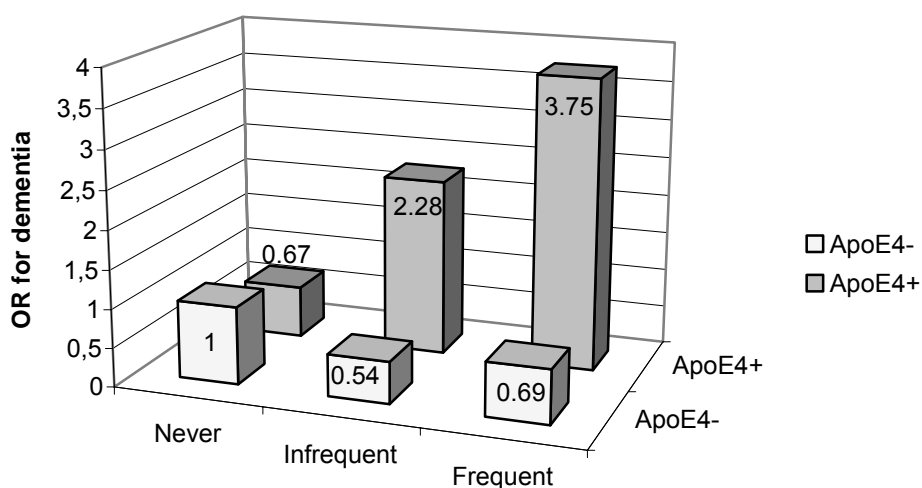
Table 13. Association between midlife alcohol drinking frequency and dementia and AD

	Odds Ratio (95 % CI)		
	Model 1	Model 2	Model 3
Dementia			
Never	1 (ref.)	1 (ref.)	1 (ref.)
Infrequent	1.02 (0.47-2.22)	1.15 (0.51-2.59)	1.09 (0.42-2.88)
Frequent	1.66 (0.70-3.92)	1.93 (0.77-4.82)	2.25 (0.74-6.83)
AD			
Never	1 (ref.)	1 (ref.)	1 (ref.)
Infrequent	0.89 (0.38-2.12)	0.94 (0.38-2.31)	0.95 (0.33-2.72)
Frequent	1.28 (0.49-3.38)	1.30 (0.46-3.64)	1.59 (0.46-5.51)
Dementia (including diagnoses for non-participants from registries)			
Never	1 (ref.)	1 (ref.)	NA
Infrequent	1.01 (0.59-1.73)	1.14 (0.66-1.99)	
Frequent	1.09 (0.58-2.04)	1.28 (0.66-2.48)	

Model 1 adjusted for age, sex, community, education and follow-up time. Model 2 adjusted additionally for midlife SBP, cholesterol, and smoking. Model 3 adjusted additionally for ApoE ε4 and late-life vascular disorders. NA= not applicable

There was a significant interaction between midlife alcohol drinking frequency and the ApoE ϵ 4 allele for the risk of dementia. The risk of dementia increased with increasing alcohol drinking frequency among the ApoE ϵ 4 carriers, while among the ApoE ϵ 4 non-carriers, the risk remained the same across the different alcohol drinking categories (**figure 3**). Similar analyses for AD yielded non-significant results. In the fully adjusted analyses stratified by the presence of the ApoE ϵ 4 allele, the risk of dementia among the ApoE ϵ 4 carriers was for infrequent drinkers 3.45 (0.84-14.11), and for frequent drinkers 6.70 (1.29-34.77). Among the ApoE ϵ 4 non-carriers there were no significant associations.

Figure 3. The combined effect of midlife alcohol drinking and ApoE ϵ 4 for the risk of dementia.



Values are odds ratios from one logistic regression analysis having the alcohol drinking frequency, apolipoprotein E ϵ 4, and interaction between alcohol*apolipoprotein E ϵ 4 in the model, and adjusted for age, sex, community, education, follow-up time, midlife SBP, cholesterol, smoking, and late-life vascular disorders. The odds ratio for the interaction term infrequent alcohol drinking*apolipoprotein E ϵ 4 is 6.34 ($p=0.04$), and for frequent alcohol drinking*apolipoprotein E ϵ 4 it is 8.07 ($p=0.03$).

Alcohol Drinking and MCI

Midlife alcohol drinking frequency was associated with the risk of developing MCI in late-life in a U-shaped manner: both never-drinkers and frequent drinkers had twice as high risk of MCI compared with infrequent drinkers (**table 14**). There were no significant interactions between alcohol drinking and ApoE ϵ 4 for the risk of MCI.

Table 14. Association between midlife alcohol drinking frequency and development of MCI

	Odds Ratio (95 % CI)		
	<i>Never</i>	<i>Infrequent</i>	<i>Frequent</i>
Model 1	2.09 (1.05-4.14)	1 (ref.)	2.29 (1.13-4.67)
Model 2	2.06 (1.02-4.17)	1 (ref.)	2.25 (1.10-4.59)
Model 3	2.15 (1.01-4.58)	1 (ref.)	2.34 (1.08-5.08)

Model 1 adjusted for age, sex, community, education and follow-up time.

Model 2 adjusted additionally for midlife SBP, cholesterol, and smoking.

Model 3 adjusted additionally for ApoE ϵ 4, and late-life vascular disorders.

Alcohol Drinking and Cognitive Functions

The next step in our analyses was to investigate the association between midlife alcohol drinking frequency and different domains of cognitive function among the non-demented participants. The never-drinkers at midlife had poorer function in the domains of episodic memory, executive function and psychomotor speed compared with both infrequent and frequent drinkers (**table 15**). Also prospective memory was poorer among the midlife never-drinkers compared with frequent drinkers.

Table 15. Cognitive functioning in late-life in relation to the midlife alcohol drinking frequency. Values are adjusted mean scores (and standard errors) from analyses of covariance (ANCOVA).

	Never	Infrequent	Frequent	p ¹ , p ² , p ^{3*}
Global cognitive functioning	26.0 (0.1)	26.2 (0.1)	26.3 (0.1)	
Episodic memory	4.9 (0.1)	5.2 (0.1)	5.2 (0.1)	p¹=0.02, p²=0.04
Semantic memory	19.7 (0.4)	20.9 (0.3)	20.7 (0.4)	p ¹ =0.08
Subjective memory	2.1 (0.0)	2.1 (0.0)	2.1 (0.0)	
Prospective memory	2.6 (0.1)	2.8 (0.0)	2.8 (0.1)	p²=0.05
Executive function	44.0 (1.4)	37.2 (1.1)	38.1 (1.4)	p¹=0.00, p²=0.01
Psychomotor speed	-0.04 (0.1)	0.19 (0.0)	0.19 (0.0)	p¹=0.00, p²=0.01

*p¹ is the p-value for the difference between never and infrequent drinkers; p² for never and frequent, and p³ is for infrequent and frequent. In the cognitive tests used, a higher result means better performance, except for the subjective memory and executive function, where the lowest result is the best performance. Bonferroni adjustment was used for multiple comparisons. Only p-values ≤0.10 are given. Model adjusted for age, sex, education, follow-up time, ApoE4, midlife vascular factors (SBP, BMI, total cholesterol, smoking) and late-life income, marital status, depression, MI, stroke, and diabetes.

In the analyses carried out separately among smokers and non-smokers, the significant results were mostly seen among the non-smokers. No differences in cognition according to the midlife drinking frequency were seen among smokers. There were significant interactions between midlife alcohol drinking frequency and smoking in episodic memory (p=0.01) and psychomotor speed (p=0.01); the cognitive performance increased with increasing alcohol drinking frequency among non-smokers, while among smokers there was no such association. There were no interactions between midlife alcohol drinking and ApoE ε4 carrier status or with alcohol drinking and sex for any of the cognitive functions investigated.

In the cross-sectional analyses in late-life, the never-drinkers in late-life performed poorer than the other two groups in executive function and psychomotor speed, and poorer than frequent drinkers in episodic and prospective memory. Furthermore, the infrequent drinkers in late-life performed poorer than frequent drinkers in episodic and prospective memory.

We could obtain more detailed information of the midlife alcohol drinking of those subjects who were included in the CAIDE-study in 1982 and 1987 (n=369). The majority of participants reported that they had not drunk beer (83 %), wine (78 %), or spirits (73 %) during the previous week.

Wine, beer or spirits drinking (weekly consumption, divided into non-drinkers, and drinkers with low and high consumption from the median value) at midlife or at late-life was not associated with any of the cognitive functions in the analyses adjusted for other beverage types, age, sex, education and follow-up time. The total weekly alcohol drinking at midlife (all alcohol types combined, categorized into three groups) was not associated with any of the cognitive functions investigated (**table 16**).

Table 16. Cognitive functioning in late-life in relation to the total weekly alcohol drinking at midlife (1982 and 1987). Values are adjusted mean scores (and standard errors) from analyses of covariance (ANCOVA).

	No	Low	High	p ¹ , p ² , p ^{3*}
Global cognitive functioning	26.1 (0.2)	25.8 (0.2)	25.8 (0.3)	All > 0.10
Episodic memory	4.9 (0.1)	5.0 (0.1)	4.8 (0.2)	
Semantic memory	19.8 (0.5)	20.0 (0.7)	20.8 (0.8)	
Subjective memory	2.1 (0.0)	2.1 (0.1)	2.1 (0.1)	
Prospective memory	2.8 (0.1)	2.7 (0.1)	2.5 (0.1)	
Executive function	39.2 (1.9)	45.7 (2.9)	46.0 (3.2)	
Psychomotor speed	0.07 (0.06)	0.09 (0.08)	0.04 (0.10)	

*p¹ is the p-value for the difference between no and low drinkers; p² for no and high, and p³ is for low and high. In cognitive tests used, the higher result means better performance, except for the subjective memory and executive function, where the lowest result is the best performance. Bonferroni adjustment was used for multiple comparisons. Only p-values ≤ 0.10 are given. Model adjusted for age, sex, education, follow-up time.

Socioeconomic Factors and Dementia

Lower education, having a physical occupation and living alone at midlife were each associated with an increased risk of developing dementia later in life in the analyses adjusted for demographic factors (**table 17**). However, when the socioeconomic factors were adjusted for each other, only low education remained as a significant risk factor. Similar findings were observed for AD. When also the follow-up non-participants were included in the analyses (diagnoses derived from patient registries), in the last model in addition to education, also living status at midlife was significantly related to the risk of dementia.

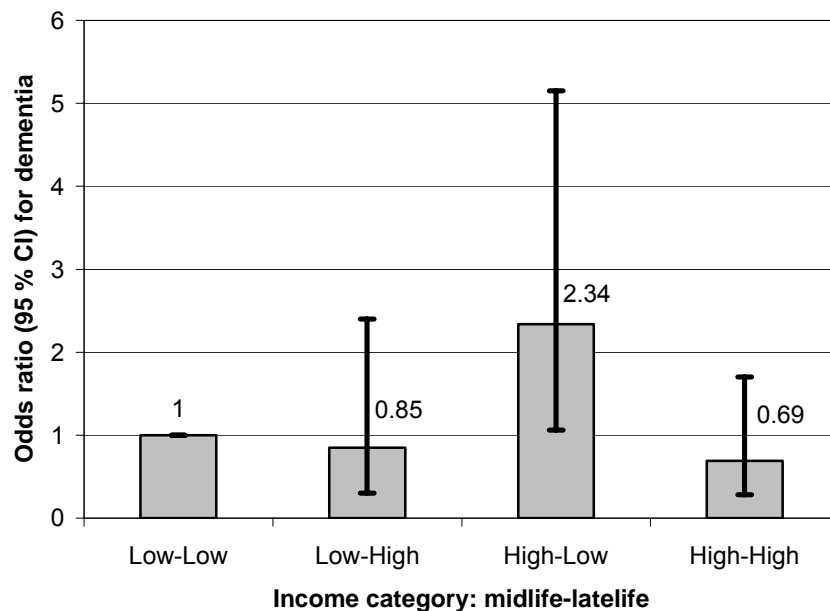
Table 17. Association between midlife socioeconomic characteristics and dementia

		Odds Ratio (95 % CI)		
		Model 1	Model 2	Model 3
Dementia				
Education, years		0.83 (0.75-0.92)	0.81 (0.73-0.91)	0.82 (0.72-0.93)
Living status, %	With partner	1 (ref.)	1	1
	Alone	1.90 (1.01-3.58)	1.84 (0.94-3.58)	1.54 (0.72-3.30)
Income level, %	Lower	1 (ref.)	1	1
	Higher	0.87 (0.40-1.54)	0.87 (0.48-1.59)	1.33 (0.70-2.53)
Occupation, %	Sedentary	1 (ref.)	1	1
	Physical	2.18 (1.15-4.14)	2.54 (1.29-4.99)	1.31 (0.60-2.88)
	No occupation	1.81 (0.92-3.59)	2.09 (1.02-4.30)	1.35 (0.62-2.95)
AD				
Education, years		0.81 (0.72-0.92)	0.80 (0.71-0.91)	0.80 (0.69-0.92)
Living status, %	With partner	1 (ref.)	1	1
	Alone	1.72 (0.85-3.61)	1.76 (0.86-3.61)	1.37 (0.59-3.16)
Income level, %	Lower	1 (ref.)	1	1
	Higher	0.89 (0.47-1.69)	0.83 (0.43-1.59)	1.24 (0.61-2.52)
Occupation, %	Sedentary	1 (ref.)	1	1
	Physical	2.23 (1.09-4.58)	2.46 (1.19-5.11)	1.14 (0.48-2.69)
	No occupation	1.79 (0.83-3.85)	1.89 (0.87-4.12)	1.15 (0.49-2.68)
Dementia (including diagnoses for non-participants from registries)				
Education, years		0.92 (0.85-0.98)	NA	0.93 (0.86-1.00)
Living status, %	With partner	1 (ref.)		1
	Alone	1.68 (1.08-2.60)		1.65 (1.02-2.66)
Income level, %	Lower	1 (ref.)		1
	Higher	0.81 (0.54-1.21)		0.99 (0.64-1.54)
Occupation, %	Sedentary	1 (ref.)		1
	Physical	1.29 (0.80-2.09)		0.86 (0.49-1.51)
	No occupation	1.72 (1.08-2.76)		1.48 (0.89-2.45)

Model 1 adjusted for age, sex, community, and follow-up time. Model 2 adjusted additionally for ApoE4. Model 3 adjusted additionally for other sociodemographic variables. NA= not applicable.

High income level in late-life was associated with a decreased risk of dementia in the analyses adjusted for demographic variables, ApoE ϵ 4 status, midlife education, occupation and living status (OR 0.36; 95 % CI 0.17-0.78). Further, the change in the relative income level between midlife and late-life examinations was also associated with dementia: compared to those persons with low income level at both times, those that reported a decrease in their income had a two-fold risk of dementia (**figure 4**). This was more prominent among men (OR 3.52; 95 % CI 0.93-13.35 for decrease in income level vs. low income at both times) than among women (OR 2.11; 95 % CI 0.74-5.97).

Figure 4. Association between change in income level from midlife to late-life and dementia



Model adjusted for age, sex, community, follow-up time, ApoE ϵ 4, education, occupation and living status.

Those participants who lived alone both at midlife and in late-life had an increased risk of dementia when compared with those who were married or lived with a partner at both time points in the analyses when adjusted for demographic factors (OR 2.15; 95 % CI 1.00-4.61). The results became attenuated when adjustments for other socioeconomic factors were applied. The loss of the partner during the follow-up time was not significantly related to the risk of dementia. There were too few persons that lived alone at midlife but with a partner in late-life to allow meaningful analyses.

Education and Dementia

In the final analyses we investigated in greater detail the association between education and dementia. The majority of the participants (53.4 %) had been at school for between 6 to 8 years. Twelve percent had been schooled for less than six years, and 34 percent had received nine years or more of education. Persons with low education were older at the late-life examination, and they had more often a lower income level, they lived alone and had a physical occupation or no occupation at all at the time of midlife examination. Further, those with low education had higher SBP, total serum cholesterol and BMI at midlife, whereas those with high education had the lowest levels of these risk factors. At late-life, those with low education had more often myocardial infarction, diabetes mellitus, and higher scores on the Beck depression scale.

Compared with those with low (0-5 years) education, the individuals with middle or high education had a decreased risk of dementia and AD (**table 18**). Adjustments for demographic factors did not change the association, nor did further adjustments for midlife lifestyles including physical activity, BMI, blood pressure, cholesterol levels and smoking. The association was slightly weaker in the model where late-life vascular disorders and depressive symptoms were added as confounding factors. However, in the final model, where we included all the confounders that were significant at least at the 10 % level in the previous models, then high education was still associated with a more than 80 % decreased risk of dementia and AD. When the analyses were repeated including also the information of the follow-up non-participants, both middle and high education were related to a decreased risk of dementia, but the point estimates were somewhat modified from the earlier analyses.

Table 18. Association between education and dementia

	OR (95 % CI)			
	Model 1	Model 2	Model 3	Model 4
Dementia				
0-5 years	1 (ref.)	1	1	1
6-8 years	0.55 (0.29-1.05)	0.59 (0.30-1.15)	0.78 (0.31-1.96)	0.57 (0.29-1.13)
9+ years	0.20 (0.08-0.47)	0.24 (0.10-0.58)	0.34 (0.11-1.06)	0.16 (0.06-0.41)
AD				
0-5 years	1 (ref.)	1	1	1
6-8 years	0.48 (0.24-0.97)	0.47 (0.23-0.96)	0.61 (0.23-1.58)	0.49 (0.24-1.00)
9+ years	0.15 (0.06-0.41)	0.17 (0.06-0.46)	0.34 (0.11-1.07)	0.15 (0.05-0.40)
Dementia (including diagnoses from patient registries for non-participants in follow-up)				
0-5 years	1 (ref.)	1	NA	1
6-8 years	0.52 (0.32-0.83)	0.52 (0.32-0.84)		0.55 (0.34-0.88)
9+ years	0.34 (0.19-0.60)	0.38 (0.21-0.69)		0.40 (0.22-0.72)

Model 1 adjusted with age, sex, follow-up time and community of residence.

Model 2 adjusted with factors in model 1 and additionally for midlife physical activity, smoking, systolic blood pressure, diastolic blood pressure, obesity and cholesterol.

Model 3 adjusted with factors in model 1 and additionally for the presence of myocardial infarction, stroke, and diabetes, and Beck depressive scale in late-life.

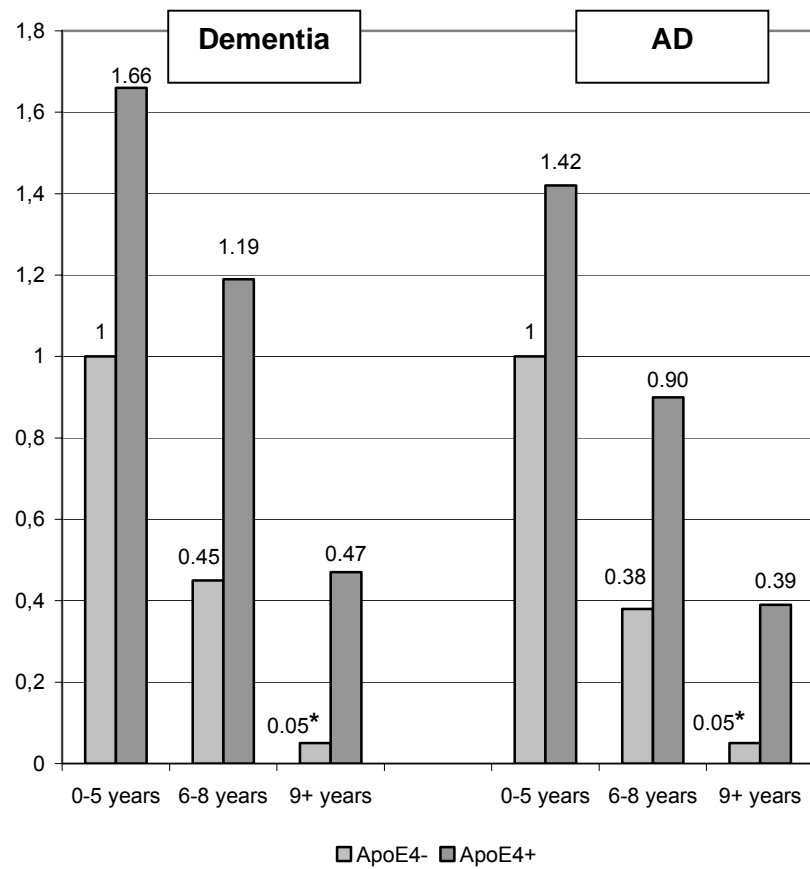
Model 4 adjusted with factors in model 1 and additionally for factors significant at least at the level of $p \leq 0.10$ in models 2-3.

NA=not applicable.

In the subgroup of persons with $MMSE \leq 24$ (who underwent the clinical phase examinations) the association between education and dementia was somewhat attenuated: those with medium education had OR 0.93 (95 % CI 0.41-2.15), and those with high education had OR 0.44 (95 % CI 0.14-1.40) compared with those with low education in analyses with adjustments as in model 4. The same ORs for AD were 0.72 (95 % CI 0.30-1.70) for medium, and 0.37 (95 % CI 0.11-1.25) for high education.

There were no significant multiplicative interactions between ApoE $\epsilon 4$ and education for the risk of dementia and AD. Among both ApoE $\epsilon 4$ non-carriers and carriers, the risk of dementia decreased with increasing education. When analysing the risk of dementia and AD in all ApoE $\epsilon 4$ *education subgroups, we observed that those who were ApoE $\epsilon 4$ non-carriers and had high education had very low odds for dementia and AD (OR 0.05 (95 % CI 0.01-0.39) for dementia, and OR 0.05 (95 % CI 0.01-0.38) for AD) when compared to the ApoE $\epsilon 4$ non-carriers with low education (**figure 5**).

Figure 5. The association between education and dementia/ AD according to the ApoE ϵ 4 status.



The odds ratios are from logistic regression models, with full adjustments. The reference group was ApoE ϵ 4 non-carriers with 0-5 years of education. * $p < 0.05$

DISCUSSION

Summary of Main Findings

This thesis investigated the role of various aspects of an individual's lifestyle on his/her late-life cognitive functions and development of dementia. The main findings can be summarised as follows:

- Obesity at midlife was associated with an increased risk of dementia and AD later in life.
- High midlife BMI, high cholesterol, and high systolic blood pressure were all significant risk factors for dementia, and they increased the risk in an additive manner.
- The presence of the ApoE ϵ 4 allele modified the association between alcohol drinking and dementia: the ApoE ϵ 4 carriers had an increased risk of dementia with increasing alcohol drinking frequency, whereas no significant effect was observed among the ApoE ϵ 4 non-carriers.
- There was a U-shaped association between alcohol drinking and MCI so that the persons, who did not drink alcohol at midlife, as well as those who were frequent alcohol drinkers, had a two-fold risk of having MCI in late-life when compared with infrequent alcohol drinkers.
- Midlife non-drinkers had poorer performance compared to infrequent and frequent drinkers in episodic memory, psychomotor speed, and executive function in late-life.
- Low income level at old age was related to an increased risk of dementia, but low income level at midlife was not. Further, decreasing income level from midlife to old age was associated with an increased risk of dementia.
- Having a sedentary occupation as opposed to having a physical occupation or no occupation at all was associated with a decreased risk of dementia. However, the association was attenuated when level of education was taken into account.
- High education was associated with lower risk of dementia and AD, and this remained unchanged after adjustments for a wide range of demographic, socioeconomic, lifestyle related, and vascular risk factors and disorders, and ApoE ϵ 4.

Methodological Aspects

Study population and design

The study is based on population-based random samples of individuals that were investigated twice during the study. The participation rates were high, ranging from 82 to 90 % at baseline and 72 % at follow-up. The prospective population-based design and relatively high participation rates increase the reliability of the findings. The follow-up time of the study was long, on average 21 years. This gave us an opportunity to investigate the risk factors that were present already at midlife.

The baseline examinations were conducted within two cardiovascular studies, the North Karelia Project and the FINMONICA study. These projects were not designed to investigate cognitive functions or dementia, and therefore we do not have information of the participants' cognitive status at midlife. However, at the time of midlife examination, the participants were from 39 to 64 years old, and it is unlikely that they would have been demented at that time. If there were persons exhibiting the early stages of dementia already at the baseline examination, probably these persons would not have survived and participated in the follow-up examination.

A random sample of the persons that had participated at the baseline examinations and had survived until 1997 were invited for the follow-up examination. In the current set of studies the information of baseline risk factors regarding those that had deceased after the initial examinations was not yet available. Therefore the possible influence of selective survival must be kept in mind when interpreting the findings, and this is discussed more in detail for each substudy. At the general level, the results are applicable to persons that survive into old age.

The study included 1409 participants, including 61 persons with dementia and 82 with MCI. This is a sufficiently large population to investigate lifestyle-related risk factors that are fairly prevalent in the population. However, in some of the sub-group analyses, as well as in the analyses regarding different alcoholic beverages where a smaller number of participants was available, we may have encountered false negative results due to insufficient power.

The possibility of bias due to the presence of confounding factors was addressed in all studies. We had information available on a wide range of demographic, socioeconomic, lifestyle and health-related factors. The main method to control for the confounding effect was to adjust the analyses for possible confounders. Additionally some of the analyses were conducted separately in sub-groups. However, there were factors about which we had no information, and some of our variables may have not been able to capture all dimensions of the phenomenon in question. Therefore there is a possibility of a residual confounding effect. This will be further considered when discussing the interpretation of the results.

Risk factor measurements

The measurements of the main risk factors of interest were done already at midlife, while the detection of dementia was carried out in late-life, on average twenty years after the risk factor assessment. Therefore, we can reasonably assume that the presence of pre-clinical dementia did not affect our measurements of midlife risk factors, which may have been the case in those studies with shorter follow-up times and with the baseline evaluation in later life. Pre-clinical dementia may have had some role in our secondary analyses that were conducted to evaluate the cross-sectional associations between late-life lifestyle factors and dementia and cognitive functions.

The information regarding BMI was based on actual measurements of weight and height, which increases the reliability of our findings and reduces the random error. Similarly, blood pressure and serum cholesterol were measured with standardized methodology, and can be considered as reliable. The data on alcohol drinking, education, occupation and income were based on self-reports. We believe that this is not a great deal problem with regards to the socioeconomic variables. However, the reliability of the alcohol drinking data is more uncertain. Earlier studies have shown that errors in reporting of alcohol drinking are in general linearly related irrespective of how one tries to assess alcohol drinking.²³⁸ Thus ranking of individuals into different alcohol drinking categories, as done in our study, should be possible. However, attention should be paid when interpreting the data regarding the risks associated with exact amounts of alcohol consumed. It is apparent that some subjects drank more alcohol than they reported. However, the difference between actual and reported alcohol drinking at midlife was probably not dependent on the future cognitive status, and therefore no bias due to misclassification of the midlife alcohol information is likely to have occurred. With respect to income data, one should bear in mind that the longitudinal analyses of income

change inquired only if the proportional status of a subject had changed compared with other subjects of the study. Therefore, the decrease and increase in income level should be understood as being relative to the entire sample, and not as an absolute change.

Outcome assessment

It would have been ideal if all the participants had gone through both screening and clinical phases of the follow-up examination. However, only those subjects scoring ≤ 24 in the MMSE in the screening phase underwent the diagnostic examinations. The three-phase protocol was probably sufficiently high in sensitivity and specificity to detect AD. Nearly half of all persons that had MMSE below the cut-off point in the screening phase were nevertheless cognitively normal in the clinical phase. This suggests that the cut-off score used was sufficiently sensitive for detecting AD in our population. The use of a higher cut-off score would have resulted in inclusion of a very large proportion of the population in the clinical phase, as the median MMSE was 26. While MMSE may have been sufficiently sensitive to capture manifest AD, the use of MMSE may have led to an underdiagnosis of other types of dementia in which memory deficits are not part of the initial manifestation of disease. Nearly all of those with dementia in the clinical phase went through brain imaging in the differential diagnostic phase. Autopsy data were not available to confirm the clinical diagnosis, but a previous neuropathologic study conducted in our clinic in Kuopio has shown that the accuracy of clinical diagnosis of AD is good (96 % for probable AD and 86 % for possible AD).²³⁹

The diagnosis of MCI in our study was essentially based on clinical judgement: the persons did not fulfill the diagnostic criteria for dementia, but had some subjective and objective cognitive impairment. Some cases of MCI and mild dementia may have been lost due to the MMSE cut-off point. The CAIDE study was essentially designed to detect dementia, and it is unclear how sensitive and specific the screening procedure was in identifying those persons with MCI. However, the prevalence of MCI in our 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.²⁴⁰

Non-participation

Non-participation may have somewhat influenced our results. We do not have information on the baseline non-participants with regards to their lifestyle characteristics or cognitive status.

However, the non-participation rates at baseline examination were very low; from 7 % in 1972 to 17 % in 1987.²²¹ The main reasons for non-participation at baseline were: address information was not up-to-date, temporarily away from home, or unable to participate. Very few individuals refused to participate.²²⁰

The role of the non-participation at follow-up examination could be evaluated to some extent. Dementia diagnoses for the follow-up non-participants were available from medical records, and these diagnoses were used in the secondary analyses to estimate the extent to which non-participation may have influenced our results. However, one must bear in mind that medical records usually underestimate the prevalence of dementia. In spite of the possible underdiagnosing, the non-participants were more often demented than the participants. Also a previous study has shown that people with cognitive decline are less likely to participate in studies.²⁴¹

The prevalence of obesity and other vascular risk factors at midlife was higher among non-participants. Hence, if the non-participants were at an increased risk of cognitive impairment and dementia, then our results would again represent an underestimation of the true effect of obesity and vascular risk factors rather than the opposite. The fact that the association between obesity and dementia remained unchanged when the non-participants were included in the analyses indicates that our main results are not due to selective participation.

Non-participants did not differ significantly from the participants in their midlife alcohol drinking frequency, and therefore the non-participation most likely did not bias the results with respect to the associations between midlife alcohol drinking and cognitive functions/MCI /dementia.

Education and income levels were lower among the non-participants and they more often had a physical occupation or no occupation. Apart from the group of having no main lifetime occupation, the effect of occupation was not significant after taking into account the information from the non-participants. In the analyses including also the non-participants, we could still observe that both those with medium and high education had a lower risk of dementia when compared to those with low education. However, the magnitude of the relative risk reduction became reduced. The reason for this could be that the persons with low education might be less likely to seek help and receive a diagnosis of dementia later than the

more educated persons. This would lead to a relatively smaller proportion of demented persons among those with low education in the patient registries thereby underestimating the risk reduction related to high education in the total sample including the non-participants. One earlier study evaluated the effect of education-selective attrition from the study, and concluded that differential loss to follow-up might influence the magnitude of the association between education and dementia, but it could not explain it away.¹⁸⁶

Results: Interpretation of the Findings

Body mass index and clustering of vascular risk factors

Our findings suggest that obesity at midlife may increase the risk of dementia and AD later in life. The association was attenuated somewhat by adjustment for other vascular risk factors and diseases, indicating that the effect of obesity on dementia might be partly mediated via these vascular factors. However, midlife obesity, high SBP, and high total cholesterol were all significant risk factors for dementia, each of them increasing the risk by around two times. Clustering of these vascular risk factors increased the risk of dementia and AD in an additive manner so that persons with all three risk factors had around a six times higher risk for dementia than persons having none of them.

Our results are in accordance with previous studies reporting an association between higher BMI and later development of dementia.¹¹⁵⁻¹¹⁷ However, some contradictory evidence does exist as well.^{113 114} The differences between the studies may be due to the differences in the genetic, demographic, and lifestyle characteristics of the populations, for example in the Japanese study, the participants were younger, and their mean BMI values were lower.¹¹⁴

Obesity is an essential feature in the metabolic syndrome, which is otherwise characterised by dyslipidemia, hypertension, glucose intolerance, and insulin resistance. Insulin resistance may be important in the pathogenesis of AD by influencing amyloid precursor protein and β -amyloid regulation, cerebral glucose metabolism, and inflammatory processes.^{94 242} When a history of diabetes at late-life was added into the analysis together with socio-demographic variables, the association between BMI and dementia became somewhat weaker but remained still statistically significant. On the other hand, the association between obesity and dementia was significant also among the non-diabetics, suggesting that diabetes may not totally explain the association. Further, nutrition and physical activity may be underlying factors for obesity,

but in the additional analyses controlling for fat intake and physical activity, the results did not change to any major extent. However we cannot rule out residual confounding. Recent evidence suggests that increased waist-hip-ratio and higher BMI would be associated with structural brain changes related to cognitive decline and dementia, e.g. with a decrease in hippocampal volume, an increase in white matter hyperintensities, and greater temporal lobe atrophy.²⁴³⁻²⁴⁵ These associations were independent of several vascular risk factors suggesting a more direct role of obesity on neurodegeneration.

It would have been interesting to have information about midlife waist-hip ratio, triglycerides, HDL- and LDL-cholesterol, glucose, and insulin levels to be able to further elucidate the apparently complex associations between vascular risk factors. Having several follow-up measurements would have allowed us to evaluate the changes occurring in these variables during the follow-up and their relation to dementia.

Our results may be somewhat compromised by survival bias. Our previous study in the same population has shown that obesity at midlife is associated with an increased mortality.²⁴⁶ Thus, if we assume that among the deceased there were more obese persons and that they would have been more likely to be demented as well, then our results would represent an underestimation of the true risk associated with obesity.

BMI is an easily available and inexpensive measurement for assessing the nutritional status of an individual, and high BMI can serve as a useful indicator of the increased risk of dementia. The effect of obesity on dementia may be partly mediated through other vascular factors. However, this does not mean that body weight control should be viewed as less important. On the contrary, lowering BMI has beneficial effects on a range of other risk factors,^{247 248} and thus, one could hypothesize that it may prevent dementia more than estimated from analyses of BMI alone. As our data has shown, the more vascular risk factors that an individual carries, the greater his/her risk for dementia and AD. Therefore, elimination of even one risk factor could decrease this risk. The role of weight reduction for the prevention of dementia needs to be further investigated.

Alcohol drinking

Our first alcohol study showed that midlife alcohol drinking was related to the risk of late-life MCI in a U-shaped manner, with both never-drinkers and frequent drinkers having a higher

risk than infrequent alcohol drinkers. This was not the case for dementia. ApoE genotype seemed to modify the association between midlife alcohol drinking and subsequent dementia as an increasing risk of dementia with increasing frequency of alcohol drinking was detected only among ApoE ϵ 4 allele carriers. These apparently different associations with regards to MCI and dementia lead us to investigate further the non-demented persons to examine how alcohol was related to different cognitive functions. We found that several domains of cognitive function, including executive function, psychomotor speed as well as episodic memory were better among the infrequent and frequent drinkers than among the never-drinkers.

Our results concerning cognitive functions and MCI are in accordance with some of the earlier findings showing that moderate drinkers perform better in certain domains of cognition.^{157 158 160 165-172} Interestingly, this type of relation has been found in different populations with respect to their alcohol drinking, and with varying definitions of moderate drinking. This may indicate that perhaps moderate lifestyles in general, which can vary across cultural environments, can protect from cognitive deterioration. Alcohol drinking might be an indicator of a more complex pattern of social and lifestyle factors, which may be difficult to determine exactly. For example, moderate alcohol drinkers may enjoy psychosocial benefits.²⁴⁹ Another possibility is that the dose-effect discrepancy across studies would be due to a large underreporting of alcohol drinking by certain populations.

The mechanisms behind the association between alcohol drinking and dementia/ cognitive functions remain unknown. Recent studies have suggested that there is a U-shaped association, i.e. beneficial effect related to moderate alcohol drinking for cardiovascular outcomes.²⁵⁰ Alcohol has a beneficial effect on several cardiovascular risk factors, including hypertension, lipid and lipoprotein levels, inflammatory and haemostatic factors,²⁵⁰ some of which are possible risk factors of poor cognitive function and dementia.²⁵¹ In the Rotterdam study,¹³⁴ the protective effect of alcohol drinking was found mainly for vascular dementia and the study indicated that one possible mechanism to explain how moderate alcohol intake would protect against dementia is via a reduction in vascular risk factors. In our study we adjusted the analyses for several cardiovascular risk factors and diseases, but this did not change the results.

The fact that alcohol drinking especially influenced measures of psychomotor speed, episodic memory, and executive function, may point to a subcortical dysfunction, and may be a result from small blood vessel and white matter lesions.²⁵² In fact, alcohol drinking has been associated with fewer brain infarcts, and to have a U-shape relationship with white matter lesions.²⁵³ White matter changes and infarcts, in turn, may imply that a vascular mechanism is responsible for the observed association between alcohol and cognitive functions.²⁵⁴

Some studies have proposed that the protective effect of alcohol would be due to the effect of specific antioxidant substances in wine.¹³⁸ This is unlikely to explain the results in our study, since the most typically consumed alcoholic beverages in Finland at the time of the study were beer and spirits. Further, the associations found for specific alcohol types showed no clear pattern for one type being better than other. Another possibility is that moderate amounts of alcohol could also act directly by releasing acetylcholine in the hippocampus.²⁵⁵

Curiously, we found that the effect of drinking on the cognitive functions appeared almost exclusively among the non-smokers, and there were statistical interactions between smoking and alcohol for episodic memory and psychomotor speed. Smoking is associated with increased oxidative stress,²⁵⁶ has a deleterious effect on the cerebral vasculature and circulation,²⁵⁷ and increases the risk of stroke.²⁵⁸ Thus one could hypothesize that in smoker these factors nullify the possible benefits of alcohol. However, these findings need to be confirmed in other studies and with experimental models before drawing any further conclusions.

In the analyses regarding alcohol drinking and cognitive functions, the differences in the test results between the groups with best and poorest performance were not very large. All participants were non-demented, and their cognitive functioning therefore within normal limits. It is difficult to estimate the impact of such small cognitive differences in an individual's quality of life.

Most of the recent population studies regarding alcohol and dementia have found an association between moderate alcohol drinking and a lower risk of developing dementia.¹³³⁻¹³⁷ However, most of the studies have not taken into account the effect of ApoE ϵ 4. Two studies have pointed to an ApoE ϵ 4 – alcohol interaction in the same direction as observed in our study.^{53 156} One possible explanation for the results could be that the ApoE ϵ 4 carriers may

have less effective neural repair mechanisms,⁵² and thus they would be more susceptible to the deleterious effect of alcohol. However, in the Rotterdam study,¹³⁴ a possible interaction between alcohol and ApoE ϵ 4 was in the opposite direction: the ApoE ϵ 4 carriers seemed to gain the benefit of the protective effect of alcohol at already lower consumption levels than the ApoE ϵ 4 non-carriers. At the moment, this topic is still unclear, and experimental studies might shed some light on the proposed interaction.

The fact that the frequent alcohol drinkers in our study were drinking only occasionally (the majority of them drank only once or twice per month), but nevertheless had an increased risk of MCI and dementia (among ApoE ϵ 4 carriers) seems contradictory to earlier findings. The difference between this present study and previous results may be attributable to different patterns of alcohol drinking in different populations. Typically, this birth cohort of Finns, particularly women, had a relatively low frequency of alcohol drinking, and the proportion of never-drinkers was higher than that in most other Western populations. Among the drinkers, it has been habitual to drink large quantities during one session, and the absolute alcohol consumption over a longer period of time was probably not very different from other populations where alcohol drinking was more frequent. It is possible, that the deleterious effect of frequent alcohol drinking seen among the ApoE ϵ 4 carriers is visible in our study because of the typical binge-drinking pattern in the (male) population; other types of heavy drinking (i.e. more frequently but not as much during any single session) may not have such detrimental effects, even among the ApoE ϵ 4 carriers. Recent findings from a Finnish twin study showed that binge-drinking is indeed associated with an increased risk of dementia.¹⁴² Excessive alcohol drinking has clear detrimental effects on brain, but it has also been shown that alcohol drinking exhibits a linear association with brain damage, starting already from light drinking levels causing an increase in brain atrophy.²⁵⁹

Our results indicate that alcohol drinking both at midlife and in late-life may be associated with several cognitive functions, including episodic memory, executive function, and psychomotor speed in late-life. In the light of our results, we suggest that the path from normal cognitive function to MCI is influenced by environmental factors e.g. frequent alcohol drinking. However, a combined effect of detrimental environmental factors and genetic susceptibility factors, such as ApoE ϵ 4, may be needed for cognitive impairment to progress further into dementia. The exact mechanisms that mediate the effect of alcohol on cognitive

status are not known. Furthermore, we cannot exclude the possibility that it would not be the effect of alcohol *per se*, but other social and lifestyle – related factors that go together with certain drinking habits that are the reasons behind the favorable association between alcohol drinking and cognitive abilities. At the moment, it is not possible to define a specific beneficial level of alcohol intake in relation to cognitive functions. Taking into account the well-known harm related to excessive alcohol drinking, and the fact that our current data indicates that frequent alcohol drinking might increase the risks of MCI and dementia, we do not want to recommend that non-drinkers should start to consume alcohol at any level.

Education and other socioeconomic factors

We investigated first the role of socioeconomic factors, including education, occupation and income level for the development of dementia. Second, we investigated further the association between education and dementia, attempting to determine whether lifestyles and other factors could explain some of the association.

We noted that decreasing income level during the follow-up time and low income level at old age were both associated with the development of dementia, but midlife lower income level was not associated with dementia later in life. This suggests that low income level may not be a risk factor for dementia but rather a consequence of the disease process. In old age, when dementia was diagnosed, all of the subjects were retired, and their income level could be considered as being stable and not influenced by the appearance of dementia. Since the disease has an insidious onset, a dementing process may have affected an individual's occupational career and income even before its full clinical manifestation. The role of income has been investigated in a few studies in addition to our own. One study showed that a low income level was associated with an increased risk of AD, but also that the effect was diluted when education was taken into account.¹⁸³

The association between the presence of dementia and the decrease in the relative income level between the midlife and old age was more pronounced among men than among women. In the questionnaire, the family income, not the personal income was enquired. Most likely men have been the primary breadwinners in the family, making the association between morbidity and family income level stronger in men than in women.

A physical occupation as opposed to a sedentary occupation was a risk factor for dementia among the participants. When the information of non-participants was included, those with no occupation had an increased risk of dementia when compared to those in a sedentary occupation. However, the associations were attenuated when information on education and income level was taken into account. Findings from the previous studies have been somewhat contradictory. One reason for this could be the fact that occupation has been defined in different ways in different studies. Manual occupation, low lifetime occupational attainment, or some occupational exposures have been shown to be associated with an increased risk of dementia.^{140 183 215 216} Other authors have failed to find any association between dementia and occupation,^{195 202 217} or various occupational exposures.^{136 140 216} In some of the studies, and in our data, the associations were attenuated when the effect of education was taken into account.^{183 203} The three occupational categories used in our study may represent a too crude and too heterogeneous grouping to permit an exact assessment of the effect of occupation on the risk of dementia.

Persons with medium to high education had a lower risk of dementia when compared to those with low education. We attempted to explain this association by examining differences in socioeconomic, vascular, or lifestyle characteristics between persons with different levels of education. However none of these factors changed the results, suggesting that the effect of education is independent of the other factors. There were no interactions between education and ApoE ϵ 4 for the risk of dementia or AD. Both of these factors affected the risk considerably, and our results show that individuals who are not ApoE ϵ 4 carriers and who have a high education have over 90 % decreased risk of dementia and AD compared to ApoE ϵ 4 non-carriers with low education.

Our results are in accordance with many earlier findings – individuals with low levels of education seem to have an increased risk of dementia and AD.^{136 140 181-190} Several hypotheses have been proposed to explain the association: the brain-battering hypothesis, the brain reserve and cognitive reserve hypotheses, and the diagnostic bias hypothesis. These will be discussed in the light of our findings.

Persons with a higher education may often have healthier lifestyles, less diseases, and may be less exposed to various toxic factors in their environment. Differences in some of these risk

factors can partially explain the differences in heart disease mortality across educational groups.²⁶⁰ Today, there is increasing evidence that vascular factors, physical activity, alcohol drinking, smoking etc. can be of importance for the development of dementia.^{63 72 96 133} According to the *brain-battering hypothesis*,¹⁹⁹ the association between education and dementia would be to a large extent due to these confounding factors. However, in our analyses, adjusting for midlife vascular and lifestyle related risk factors did not change the association between education and dementia. In the model including late-life diseases, the results were somewhat attenuated. The persons with low levels of education also had more often stroke, myocardial infarction, diabetes and more depressive symptoms, and perhaps partly the effect of education could be mediated via these factors. Only a few other studies have investigated the brain-battering hypothesis. The EURODEM pooled analysis, the Kungsholmen project, and some cross-sectional studies have controlled their analyses for alcohol or smoking and vascular diseases, but they still found significant association between education and dementia.^{181 197 209 261} However the follow-up times were only up to 3 years, and it cannot be excluded that lifestyles and vascular characteristics would have changed as a result of sub-clinical dementia. The Framingham study with a follow-up of 17 years showed that the association between education and non-AD dementia was attenuated when information about smoking was taken into account.¹⁹²

According to the *brain reserve hypothesis*,²⁶² individuals with higher levels of education have greater reserve capacity, and thus greater pathological changes are needed to reach the threshold for clinically manifest dementia than is the case in individuals with less education and a lower reserve capacity. This brain reserve could be innate or due to factors in early life, and prolonged education would merely be a consequence of having a greater reserve. The concept of *cognitive reserve*²⁶³ adds a more functional component to the brain reserve hypothesis: the reserve could be seen also as a more efficient and/ or flexible way of using the existing networks to process tasks. The variability in the amount of cognitive reserve between persons could be both genetic and as a result of lifelong mental stimulation due to education, occupation, leisure activities etc.

In addition to a low level of education, also low prestige occupation and a lack of leisure activities seem to be associated with an increased risk of dementia and AD,^{56 194 202} though the results across studies are somewhat contradictory.^{183 203 217} When we investigated if the association between education and dementia was due to lifelong mental activity, we did not

observe any change in the association between education and dementia. Of course, we acknowledge that our variables (occupation, income, and living status) were not able to capture all dimensions of mental stimulation; we had for example no detailed information on hobbies, social network, or mental demands of the work.

Our findings can be interpreted as being in line with the reserve hypotheses. However, we did not have the possibility to evaluate the effect of factors that reflect brain maturation. Education could either be a result of having a greater reserve to begin with, or attributable to education itself which could create an additional reserve against the clinical manifestation of dementia. While the construct of reserve is a useful means of conceptualising the dilemma between pathology and clinical manifestation, the unanswered question is whether the reserve is innate, or due to childhood factors, or can even later experiences such as those related to education and occupation provide more reserve. There is some evidence that factors present early in life, such as childhood IQ, linguistic ability, or early-life socioeconomic status would be related to the risk of developing dementia and AD,^{213 264-266} but findings so far are contradictory.²¹⁸ Head size, and intelligence have even been suggested to explain or modify the association between education and dementia.^{194 198} Genetics could account for a large proportion of the variance even in late-onset AD.^{267 268} However results from one twin study, the design of which controlled for genetic and other familial influences, found that education still was associated with AD,¹⁵³ though another twin study was inconclusive.²⁰¹ Animal studies suggest that even aged animals can benefit from an enriched environment.²⁶⁹ Currently, it is not clear whether this is the case in humans too - the few studies on cognitive training have shown a beneficial effect on the trained cognitive abilities, but no effect on cognitively demanding everyday functions.²⁷⁰ Thereby it still remains an open question as to whether educational interventions or cognitive training can be relevant for the prevention or postponement of dementia.

Studies with autopsy data have shown that while education is associated with clinical AD, it is not related to neuropathological changes.¹⁹⁸⁻²⁰⁰ It has been proposed, that education could affect the appearance of dementia in individuals with underlying dementing illness, and that there could be two sets of risk factors: those related to pathology and those related to clinical expression, whether it is described in terms of reserve or not.¹⁹⁸ A recent study has even shown that education (or something related to education) affects the association between AD pathology, especially plaque formation, and cognitive function.^{271 272}

It has also been proposed that a *diagnostic bias* would account for the observed association between education and dementia.²⁷³ Education provides skills that enable educated individuals to perform better in the neuropsychological tests used for screening of dementia, and this may lead to an under-representation of educated persons among the demented. We attempted to investigate the possibility of diagnostic bias resulting from the screening method by limiting the analyses to a subgroup of screening positive persons who underwent the detailed diagnostic examinations. The results showed that the odds ratios for both dementia and AD still decreased with increasing education, but the differences were not as great as in the main analyses, and were no longer statistically significant. This suggests that perhaps diagnostic bias can to some extent influence the observed associations. However, the number of subjects in the subanalyses might have been too small to detect significant associations. An earlier study investigating the role of test bias due to use of MMSE as a screening test found that the use of MMSE resulted in higher odds ratios for the low education - dementia association, but that this influence did not completely explain the association.¹⁸⁶ Further, one must bear in mind that possibly those better educated individuals that scored low on the MMSE test suffer from a more advanced dementia²⁷⁴ thereby leading to an underestimation of the true protective effect of education.

The current analyses are based on a sample of persons that survived until the time of re-examination. However, it is known that persons with low education suffer also higher mortality.²⁷⁵ If those that died between the examinations also were more often demented, then our results would underestimate the true association between education and dementia.

Our results reconfirm that high education is related to a lower risk of dementia and AD. We found that the association was independent of a wide range of other vascular and lifestyle related risk factors. Educated persons may have greater cognitive reserve that leads to a postponement of the clinical manifestation of dementia. Unhealthy lifestyle options may independently contribute to the depletion of this reserve or directly to the underlying pathologic processes. Whether this cognitive reserve is created during brain maturation (and therefore mostly related to genes, pregnancy and early life environment), or whether education as well as other mental stimulation later in life can create additional reserve against the clinical manifestation of dementia, would require studies of cohorts with information extending from before birth to old age.

Conclusions

Our set of studies showed that several modifiable lifestyle-related factors at midlife may affect the later development of dementia and AD. In summary, midlife obesity was associated with an increased risk of dementia and AD, however this association might be partly mediated through other vascular risk factors. Midlife obesity, a high total cholesterol level, and high blood pressure were all independently associated with an increased risk of developing dementia and AD later in life. Further, clustering of these factors increased the risk of dementia and AD in an additive manner.

Alcohol drinking at midlife was associated with the risk of dementia especially among the ApoE ϵ 4 carriers. Among these individuals, the risk of dementia increased with increasing alcohol drinking frequency. On the other hand, midlife alcohol drinking was associated with the development of MCI in a U-shaped manner. Further, among the non-demented population, the alcohol drinkers had better performance in several domains of cognitive function compared to abstainers. However, it is not clear whether this association is causal, or what would be a safe limit of drinking to achieve the best cognitive function.

High education was associated with a decreased risk of dementia, and lifestyle-related or sociodemographic factors could not explain the association. On the other hand, education could account for the association that was observed between a sedentary occupation and decreased risk of dementia. Educated persons might have a greater cognitive reserve that leads to a postponement of the clinical manifestation of dementia. An unhealthy lifestyle may independently contribute to the depletion of this reserve or directly induce the pathologic processes underlying AD and dementia. A reduction in income level between midlife and late-life was more frequent among the demented, and it might be a consequence of the dementing disease process.

Implications and Future Perspectives

At the moment, there is no curative treatment for dementia and AD, and already today dementia is a major challenge to the public health. As life expectancy is increasing and more and more people live to a very old age, the prevalence of dementia is expected to increase dramatically. If we are to influence the future occurrence of dementing diseases, then we need to identify effective preventive measures. The evidence is accumulating that lifestyle-related factors are related to the development of dementia including also AD. This may open avenues for the prevention of dementia and AD.

Obesity is on the increase across the world with its severe consequences on cardiovascular health. BMI is an easily available and inexpensive measurement, and high BMI can serve as a useful indicator of the increased risk of dementia. Lowering BMI has beneficial effects for a wide range of other risk factors, and thus, one could hypothesize that it may prevent dementia more than estimated based on the findings for BMI alone. So far, it has not been investigated if weight reduction can affect the risk of dementia. Furthermore, the timing of weight reduction might be important (midlife versus late-life), but this issue will need to be determined in future studies.

Alcohol drinking is on the increase all over the world. Harmful drinking patterns are common worldwide, and the historically more healthy patterns of drinking are deteriorating, which underlines the importance of the health problems related to alcohol drinking. Moderate alcohol drinking may be associated with a decreased risk of dementia and better cognitive function. At the moment, it is still doubtful if the effect of alcohol is truly due to alcohol or to some other social and lifestyle factors. There is evidence that binge drinking is associated with negative cardiovascular outcomes, and possibly also with an increased risk of dementia. The role of drinking patterns for the development of dementia needs to receive more attention in the future. The interaction between ApoE ϵ 4 and alcohol that we revealed in our study suggests that the association between alcohol and dementia is more complex than earlier believed. Experimental studies might shed some light on the issue. At the moment there is no evidence to indicate that starting to drink at a later age would be beneficial. On the other hand, there is no reason to recommend abstinence to those who drink in moderation.

Education is inversely associated with the risk of dementia and AD. However, it is unclear whether education only reflects innate or early-life factors, or whether education itself can create additional reserves that protect from dementia. The education levels are increasing, and if education does protect from dementia, the incidence of dementia should decrease in the years to come. Animal studies have suggested that exposure to an enriched environment increases the cortical thickness and number of synapses. Whether this can be transferred to humans, for example in the form of cognitive training, remains an interesting task for future research.

In this work we focused not only on lifestyle-related factors but also on interactions between genes and the environment. In addition to our findings with respect to alcohol, also other recent studies suggest that ApoE ϵ 4 carriers would be more vulnerable to a variety of environmental factors. For example it has been shown that the associations between physical inactivity or saturated fat intake and an increased risk of dementia are more pronounced in ApoE ϵ 4 carriers.^{63 122} Further investigation of these gene-environment interactions both in epidemiologic and experimental settings may increase our understanding of the disease process.

Several separate risk factors of dementia have been identified in epidemiologic research. As each individual has a set of various risk and protective factors, an approach of trying to assess the absolute risk levels of an individual by taking all his/her characteristics into consideration could represent the next step. This is already a reality in the field of cardiovascular research, where practical tools based on research findings have been developed for physicians and patients. This could be done for dementia and AD as well.

The evidence is starting to accumulate that the role of several risk factors might be dependent on the life-period: early life – midlife – late-life. Therefore the life-course perspective might prove to be important in future studies. So far the epidemiologic evidence comes mostly from cross-sectional studies, and prospective studies conducted in old age, or in some cases with also midlife data available. It will be a challenge in the future to conduct studies that cover the whole lifespan, from the cradle to the grave.

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