

*Helsinki University  
Biomedical Dissertation no. 153*



*DETERMINANTS OF COGNITIVE IMPAIRMENT IN OLD AGE  
AND THEIR GENETIC ARCHITECTURE*

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*ACADEMIC DISSERTATION*

*To be presented with the permission  
of the Medical Faculty of the University of Helsinki  
for public examination  
in the Hjelt Institute  
Mannerheimintie 172, Helsinki  
on 29<sup>th</sup> June 2011 at 12.00*

*Helsinki 2011*

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*Muistin hiljaa hiipuessa ja ajatuksen juoksun hidastuessa*

*alkavat tunteet ja tarinat elää  
naurussa, laulussa, nyrkeissä, syleissä,  
unissa, joita nähdään öin ja valveilla.*

*Ja vaikka jaloista pyrkimyksistämme huolimatta*

*omakin muistimme pettäisi meidät,  
muistaisin minä Sinut silti:  
rohkaisusi, uskosi, yhteisen innostuksemme,  
paloja mahdollisuuksien maailmasta,  
ehkä juuri tämän päivän.*

*Cover graphic: Elina Ketola*

*ISSN: 1457-8433*

*ISBN: 978-952-10-7053-2 (paperback)*

*ISBN: 978-952-10-7054-9 (pdf)*

*<http://ethesis.helsinki.fi>*

*UniGrafia*

*Helsinki 2011*

## *Abstract*

Cognitive health is of central importance for independent and balanced old age, while memory disorders represent the leading cause of intensive and long-term care among the Finnish elderly. Both aging of the population and the lack of effective disease modifying treatments for memory disorders highlight the importance of studies on the determinants of cognition in old age.

Little is known about the effect of the childhood living environment on cognition in old age, but it is reasonable that the basis for the cognitive capacity and reserve is already formed at younger ages. Moreover, the encountered exposures and the life-style during adulthood set the basis for well-being in old age, including cognitive health.

The aims of this study were to analyse the effect of height, considered as an indicator of the childhood environment, the body mass index, weight change, metabolic conditions and coffee drinking in midlife on cognitive performance in old age among a sample of 2606 Finnish twins aged 65 years or older who had participated in a telephone interview to assess their cognitive status. A twin design was used to examine the source of interindividual variation and causal relations between factors associated with cognitive impairment. Since coffee drinking associates with several metabolic conditions and Finns are known to be the greatest consumers of coffee in the world, the heritability and stability of coffee drinking was analysed in the whole Older Finnish Twin Cohort. In order to investigate the association between height and cognitive performance in a population with different childhood living conditions, a total of 2161 Danish twins were included in this study.

A greater height was found to clearly associate with better cognitive performance in Finnish subjects, but less so among the Danish sample, which may reflect the childhood environmental differences between these cohorts. In the Finnish subjects, there was greater variance in cognitive performance among shorter subjects, and environmental factors were found to play a greater role in their cognitive performance, whereas the cognitive performance of taller participants was mainly explained by genetic factors.

Midlife metabolic variables that were found to be significantly associated with a poorer cognitive performance in old age included a higher body mass index and three metabolic conditions: cardiovascular disease, hypertension and, most significantly of all, diabetes. Moreover, both weight gain and loss, even to a lesser degree than suggested previously, were found to be associated with poorer cognition. Furthermore, evidence of a causal relationship between midlife cardiovascular disease and cognitive performance in old age was demonstrated among discordant twin pairs. Conversely, no effect of coffee drinking in midlife on cognitive performance in old age was observed, although coffee drinking was demonstrated to be stable in the study population. The heritability of coffee drinking was found to differ across sexes and age groups, being 51% in men and 52% in women in the whole study population.

This study supports the contention that cognitive performance in old age reflects the effects of multiple genetic and environmental exposures, including their complex interactions during the life-span. The demonstrated associations and evidence of a causal pathway between potentially preventable exposures and poorer cognitive performance highlight the importance of preventive medicine.

## *Tiivistelmä*

Tiedon käsittelystä eli kognitiosta vastaavien aivotoimintojen terveys on keskeistä itsenäisen ja mielekkään ikääntymisen kannalta. Vaikea-asteinen kognition heikentyminen on yleisin syy suomalaisten vanhusten pitkäaikaiseen laitoshoitoon. Väestön ikääntyminen ja rajalliset mahdollisuudet vaikuttaa muistisairauksien etenemiseen korostavat kognition heikentymisen riski- ja suojatekijöiden tutkimisen tärkeyttä.

Lapsuusiän elinolosuhteiden vaikutuksesta vanhuusiän kognitioon tiedetään vasta vähän, mutta aivojen kehittymistä koskevan tiedon perusteella voidaan olettaa, että kognitiivinen kapasiteetti ja tiedonkäsittelyn varannot kehittyvät oleellisesti jo elämän varhaisvuosina. Toisaalta myös aikuisuudessa esiintyvät ympäristötekijät ja osittain valittavissamme olevat elintavat vaikuttavat vanhuusiän kognitiiviseen terveyteen.

Tutkimuksen tavoitteena oli selvittää miten aikuisiän pituus, jonka oletettiin heijastavan epäsuorasti lapsuusiän elinolosuhteita, painoindeksi, painon muutos, aineenvaihdunnalliset sairaudet ja kahvin juonti vaikuttavat vanhuusiän tiedonkäsittelyyn. Tutkimusaineisto koostui 2606:sta vanhempaan suomalaiseseen kaksoskohorttiin kuuluvasta vähintään 65-vuotiaasta kaksosesta, joille suoritettiin kognitiota mittaava puhelinhaastattelu. Kaksosuuutta hyödynnettiin tutkimalla yksilöiden välisten erojen taustaa ja kartoitettaessa tutkimuksessa havaittujen yhteyksien syyseuraussuhteita. Koska kahvin juonnilla tiedetään olevan vaikutusta useisiin aineenvaihdunnallisiin sairauksiin ja suomalaiset ovat tunnettuja kahvin suurkuluttajia, selvitettiin myös kahvin juonnin perinnöllisyys eli geneettisten tekijöiden osuus yksilöiden välisissä eroissa kahvin juonnissa sekä perinnöllisen osuuden muuttuminen iän mukana koko vanhemmassa suomalaisessa kaksoskohortissa. Tutkimukseen otettiin mukaan myös 2161 ikääntynyttä tanskalaista kaksosta, koska pituuden ja vanhuusiän kognition välistä yhteyttä haluttiin tutkia myös suotuisammissa olosuhteissa varttuneella väestöllä.

Tutkimuksessa havaittiin, että pidemmällä henkilöillä oli useimmiten parempi kognitiivinen suorituskky vanhuusiässä, kun taas heikompi suoriutuminen kognitiota mittaavassa testissä oli yleisempää lyhyempien joukossa. Pituuden ja kognition välinen yhteys oli selkeämpi

suomalaisessa kuin tanskalaisessa aineistossa, mikä saattaa johtua suomalaisen kohortin kasvuiän aikaisista epäsuotuisista ympäristötekijöistä. Ympäristötekijät selittivät suuremmassa määrin lyhyempien suomalaisten vanhuusiän kognition eroja, kun taas pidempien suomalaisten erot johtuivat pääosin geneettisistä tekijöistä.

Keski-ikänsä suurempi painoindeksi, sokeritauti, sydänverisuonisairaus ja verenpainetauti olivat tilastollisesti merkitsevästi yhteydessä heikompaan kognitiiviseen suoriutumiseen vanhuusiässä. Myös aiemmin havaittua vähäisempi keski-ikänsä painon nousu ja lasku liittyivät heikompaan suoriutumiseen kognitiota mittaavassa haastattelussa. Kaksosparin sisäinen tutkimusasetelma tuki syysseuraussuhteen olemassaoloa keski-ikänsä sydänverisuonitautin ja vanhuusiän kognition välillä. Kahvin juonnilla keski-ikänsä ei kuitenkaan havaittu olevan itsenäistä vaikutusta vanhuusiän kognitioon, vaikka kahvin juonnin osoitettiin muuttuvan suhteessa ikään vain vähän. Geneettisten tekijöiden selitysosuus yksilöiden kahvin juonnin eroissa oli suomalaisilla miehillä 51% ja naisilla 52%.

Tutkimuslöydökset vahvistavat käsitystä siitä, että vanhuusiän kognitiivinen suorituskyky heijastaa useita geneettisiä ja ympäristöstä johtuvia tekijöitä sekä näiden monimutkaisia vuorovaikutuksia. Havaitut yhteydet ja viitteet syysseuraussuhteiden olemassaolosta mahdollisesti vältettävissä tai hoidettavissa olevien riskitekijöiden osalta korostavat ennaltaehkäisevän lääketieteen merkitystä kognition heikentymisen ehkäisyssä.

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Telephone interview for cognitive status

Original publications

## *Abbreviations*

|                  |  |
|------------------|--|
| A                | additive genetic factors   |
| A $\beta$        | amyloid found in AD patient's brain  |
| AD               | Alzheimer's disease  |
| ALDH2            | aldehyde dehydrogenase, an enzyme involved in alcohol metabolism   |
| APP              | amyloid precursor protein  |
| APO $\epsilon$ 4 | genetic allele associated with greater risk for dementia   |
| BMI              | body mass index (kg/m <sup>2</sup> )   |
| BP               | blood pressure   |
| C                | shared i.e. common environmental factors   |
| CI               | confidence interval  |
| CNV              | copy number variant, alteration of genomic DNA that corresponds to relatively large regions of the genome that have been deleted or amplified on certain chromosomes |
| CSF              | cerebrospinal fluid  |
| CT               | computed tomography  |
| CYP1A2           | cytochrome P450 enzyme, responsible for caffeine metabolism  |
| D                | dominant genetic factors   |
| DLB              | dementia with Lewy bodies  |
| DZ               | dizygotic  |
| E                | nonshared i.e. unique environmental factors  |
| FTD              | frontotemporal dementia  |
| G $\times$ E     | interaction between genes and environment  |
| H <sup>2</sup>   | broad-sense heritability, proportion of variance due to genetic factors  |
| h <sup>2</sup>   | narrow-sense heritability, proportion of variance due to additive genetic factors  |
| HDL              | high-density lipoprotein   |
| LSADT            | Longitudinal Study of Aging Danish Twins   |

|                |   |
|----------------|---|
| MCI            | mild cognitive impairment, diagnostic criteria formulated by Mayo Clinic Alzheimer's Disease Research Center (MCADRC) |
| mixed dementia | memory disorder whose neuropathological findings include AD and typical vascular lesions                              |
| MMSE           | Mini-Mental State Examination, a screening test for cognitive function  |
| MRI            | magnetic resonance imaging  |
| MZ             | monozygotic   |
| OR             | odds ratio  |
| p-tau          | hyperphosphorylated form of microtubule-associated protein tau  |
| PDD            | Parkinson's disease dementia  |
| PET            | positron emission tomography  |
| $r_A$          | correlation of additive genetic factors   |
| SD             | standard deviation  |
| SES            | socioeconomic status  |
| SNP            | single nucleotide polymorphism  |
| SPECT          | single photon emission computed tomography  |
| T2DM           | type two diabetes mellitus  |
| TELE           | telephone interview for cognitive status  |
| TICS           | telephone interview for cognitive status  |
| VaD            | vascular dementia   |

## *List of Original Publications*

- I Laitala VS, Kaprio J & Silventoinen K 2008, Genetics of coffee consumption and its stability, Addiction 103(12): 2054-2061.*
- II Laitala VS, Kaprio J, Koskenvuo M, Riih  I, Rinne JO & Silventoinen K 2009, Coffee drinking in middle age is not associated with cognitive performance in old age, American Journal of Clinical Nutrition 90(3): 640-646.*
- III Laitala VS, Kaprio J, Koskenvuo M, Riih  I, Rinne JO & Silventoinen K 2011, Association and Causal Relationship of Midlife Obesity and Related Metabolic Disorders with Old Age Cognition, Current Alzheimer Research 8(6), e-pub 00057.*
- IV Laitala VS, Hjelmborg J, Koskenvuo M, Riih  I, Rinne JO, Christensen K, Kaprio J & Silventoinen K, Shorter Adult Stature Increases the Impact of Risk Factors for Cognitive Impairment, A comparison of Two Nordic Twin Cohorts, submitted.*

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## 1. Introduction

Although cognitive impairment has been associated with multiple organic and even more psychiatric conditions during the past, acquired cognitive impairment was described only in the 1600s by the Englishman Thomas Willis (1621–1675). He also considered age as a risk factor for this condition, which was still referred to as “morosis”, “stupidity” or “foolishness” in his time. *Amentia senilis* was first described in the 1700s by the Scottish physician William Cullen (1710-1790), who described it as “imbecility of judgement, by which men either do not perceive the relation of things or forget them due to diminished perception and memory when oppressed by age.” However, dementia was considered more as a part of normal aging than an independent disease until the end of the 1800s when both macro- and microscopic examination of the brain started reveal neuropathological lesions associated with specific diseases (Haltia 2010).

Today, the word dementia indicates cognitive impairment ensuing from organic dysfunction and interfering with daily activities. The most common cause of dementia is Alzheimer’s disease (AD), which was first described by Alois Alzheimer (1864-1915) in 1907. He identified four hallmark features of AD in the brain of his patient Auguste D, a 51-year-old woman who had suffered from progressive cognitive impairment, hallucinations, delusions and severely impaired social functioning during 5 years (Ferri et al. 2005).

Nowadays, dementia is considered as one of the most burdensome conditions of later life. In high-income countries, AD and other dementias are the fourth leading contributors to the burden of diseases measured by the equivalent number of lost years of full health (DALYs), representing approximately 4% of DALYs in 2004 (World Health Organization 2004). Since troubles with daily activities in dementia eventually lead to the loss of independence and need for help, memory disorders also represent the leading cause of intensive and long-term care among the Finnish elderly, while care and nurture represent 80-85% of the costs of dementia. Taking account the aging of the population and especially the rapid increase in the proportion of oldest old, the costs of dementia are likely to increase in the future. Thus, when also considering the economic aspects, the prevention and early detection of dementia is important (Martikainen et al. 2010).

In addition to developed countries, life expectancy and the prevalence of diseases, such as dementia, that are associated with old age are also expected to increase in low-income countries. Since dementia, like most other common diseases, is likely to result from an interplay of multiple genetic and environmental exposures (Rothman and Greenland 2005), a life-time perspective in terms of the prevention of dementia is important: the determinants of dementia may already be encountered prenatally and in the early years of life (Borenstein et al. 2006), although the exposures of mid- and later life have been studied more. As a result of intensive and multidisciplinary studies, several (potential) determinants of dementia have currently been established. However, only little is known about the complex interaction among them.

## *2. Review of the literature*

### *2.1 Impaired cognition and dementia*

Both dementia and mild cognitive impairment (MCI) are terms used to describe a set of symptoms that may result from various pathological mechanisms. In MCI, subjective symptoms of cognitive impairment (affecting either memory or other cognitive domain/domains, such as language, praxis, visual perception and most notably executive function) coincide with the objective impairment of cognitive function, although the performance of daily activities is not affected and the diagnostic criteria of dementia or any specific memory disorder are not fulfilled (Erkinjuntti et al. 2010). However, both in practice and epidemiological studies, a variety of related terms, such as mild impairment of cognitive function, without precise or consistent criteria are used to describe cognitive impairment that is less severe than dementia.

In dementia, cognitive impairment affects more than one cognitive domain and interferes with an individual's ability to perform work, social and/or daily activities. Although cognitive impairment in dementia may be a stable sequel (e.g. resulting from cerebral infarction), a result of progressive disease, such as AD, or may manifest as a treatable organic dysfunction (such as hypothyroidism), it always ensues from an organic malfunction (Erkinjuntti et al. 2010). Progressive memory disorders leading to cognitive impairment and eventually to dementia are discussed later.

In tandem with the aging of the population and an increase in life expectancy, dementia places a tremendous burden on patients, care-givers and society. As a consequence, dementia is of growing interest to medical professionals and the public. Since it will probably be easier to stop the damage than to undo it, understanding the pathophysiology of the causes of dementia and their prevention is of main interest (Kester and Scheltens 2009).

### *2.1.1 Epidemiology and aetiology*

Dementia is rare in the young and middle-aged, but after the age of 50 years it becomes increasingly common, with a sharply rising incidence after the age of 65. According to a Finnish study, which determined a prevalence of 5.3% for MCI among the Finnish elderly aged 60 to 76 years in 1998, approximately 120 000 Finnish individuals suffered from MCI at that time (Hänninen et al. 2002). In the same year, approximately 35 000 Finns suffered from mild and 85 000 from moderate or severe dementia, while the annual incidence of dementia was at least 12 000 new cases (Viramo and Sulkava 2010). Taking into account the aging of Finnish population, the number of patients with moderate or severe dementia in 2020 will be approximately 115 400, assuming no differences in the prevalence rates (Sulkava 2005).

According to three extensive nationwide Finnish studies, the Mini-Suomi study (Sulkava et al. 1985), the Helsinki Aging Study (Juva et al. 1993) and the Kuopio 75+ study (Koivisto et al. 1995), the overall, pooled prevalence of severe and moderate dementia in the Finnish population is 4% in 65- to 74-year-olds, 11% in 75- to 84-year-olds and 35% in people aged 85 years or older (Sulkava 2005).

International prevalence studies have tended to yield slightly different results depending on the methods used. A collaborative study of 11 population-based European cohorts and a total of 2346 cases of mild to severe dementia recorded a pooled prevalence for men and women, respectively, of 1.6% and 1.0% for those aged 65–69 years, 2.9% and 3.1% for 70–74-year-olds, 5.6% and 6.0% for 75–79-year olds, 11% and 12.6% for 80–84-year olds, 12.8% and 20.2% for 85–89-year-olds, and 22.1% and 30.8% for those aged 90 years or older (Figure 1) (Lobo et al. 2000). Another collaborative study reported higher incidences of dementia in northern compared to southern European countries (Fratiglioni et al. 2000). The higher prevalence of dementia in Finnish studies may reflect high incidence of cardiovascular diseases, high prevalence of the apoε4 allele (Polvikoski et al. 2001) and low educational level among older Finnish birth cohorts. In addition, variation in detection and differences in diagnostic criteria between countries cause large differences in prevalence rates (Erkinjuntti et al. 1997, Berr et al. 2005).



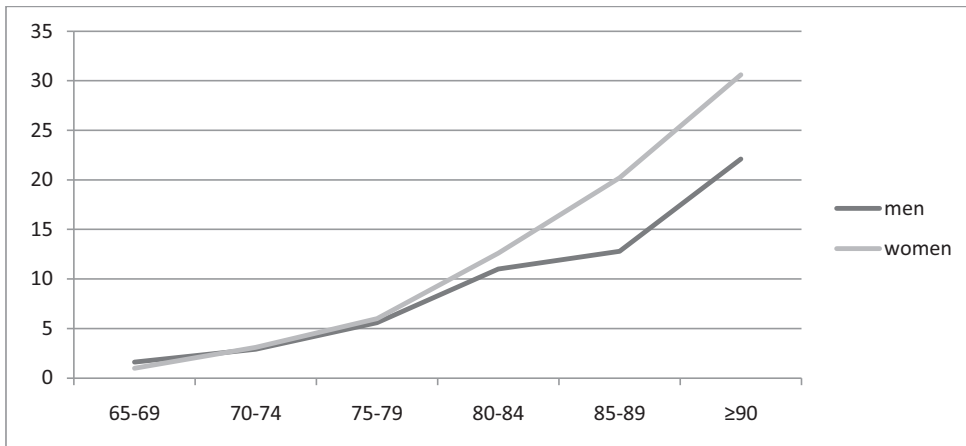


Figure 1. Pooled prevalence (%) of all dementia as a function of age and sex. The data comprise subjects from eight European countries (Lobo et al. 2000).

There is also ethnic variation in the causes of dementia; AD represents the largest proportion of dementia cases in northern and western Europe, and the prevalence of a vascular aetiology is highest in Asia (Viramo and Sulkava 2010). However, due to the variability in the clinical picture, the high frequency of mixed pathologies and methodological differences in diagnosing AD (Erkinjuntti et al. 1997, Berr et al. 2005) and vascular dementia (VaD) (Jellinger 2008), there is a lack of agreement regarding their epidemiology and prevalence. Nevertheless, the main pattern of dementia subtypes is similar across the world, with AD accounting for 50 to 70% and VaD for 15 to 25% of all dementia cases (Qiu et al. 2009). In addition to the high prevalence of cerebral amyloid angiopathy, vascular lesions were found in the brain of 57% of autopsy-verified AD cases, suggesting a high frequency of mixed pathologies (Jellinger and Attems 2005). However, in neuropathological studies, the prevalence of mixed dementia has also ranged widely from 0 to 55% due to differences in diagnostic criteria (Zekry et al. 2002).

In addition to AD, VaD (including subcortical ischemic vascular disease, multi-infarct dementia and strategic infarcts) and their mixed form, other leading memory disorders include dementia with Lewy bodies (DLB, accounting for approximately 10% of autopsy cases), which often coincides with AD, and frontotemporal lobar degenerations, including frontotemporal dementia (FTD, includes Pick's disease), progressive nonfluent aphasia and semantic dementia (together accounting for less than 5% of autopsy cases). Together, they

account for approximately 95% of memory disorders (Viramo and Sulkava 2010). In addition, Parkinson's disease dementia (PDD), other extrapyramidal diseases (including progressive supranuclear palsy, corticobasal degeneration, Huntington's disease and multisystem atrophy) and prion diseases are considered as memory disorders. Familial causes constitute up to at least 5 to 10% of dementia cases and are more often associated with earlier onset (Kumar et al. 2007). Furthermore, in addition to remediable symptoms, traumas, infections, endocrine diseases, nutritional deficits and substance abuse may lead to permanent memory and cognitive impairment, although they are not considered as memory disorders.

### *2.1.2 Pathology*

Dementia is a phenotype ensuing from several diseases, each of which presents with distinctive pathophysiological features. However, in the brain of dementia patients, multiple pathological lesions originally associated with different diseases are often detected, and pathological mechanisms underlying different causes of dementia are partly similar. In terms of prevention, this means that both protective and risk factors for dementia may be similar, regardless of the specific aetiology, and studying the determinants of dementia does not necessarily require a precise diagnosis of the underlying disorder.

AD is characterized by the presence of neuronal loss, glial reaction, extracellular plaques and intracellular neurofibrillary tangles in the brain. Plaques consist a core of  $\beta$  amyloid ( $A\beta$ ), which is a peptide derived from a larger amyloid precursor protein (APP) by enzymes called  $\beta$ - and  $\gamma$ -secretases, alternatively to the formation of an "innocent" solute by  $\alpha$ - and  $\gamma$ -secretases. Microglial cells and reactive astrocytes usually surround the  $A\beta$  core, but these  $A\beta$  deposits can also be found without any surrounding neuritic reaction, termed diffuse plaques, which are also detected in the brains of healthy elderly people. Neurofibrillary tangles are bundles of paired helical filaments mainly consisting of hyperphosphorylated forms of microtubule-associated protein tau (p-tau), and are also found in other degenerative diseases (Kumar et al. 2007).

A decreased  $A\beta$  level and increased levels of tau and P-tau in cerebrospinal fluid (CSF) are associated with AD, and are evident even years before the onset of symptoms (Herukka et al.

2005). Similarly, typical macroscopic lesions for AD patients can also be detected within the brains of asymptomatic twin siblings (Järvenpää et al. 2003) and people suffering from mild cognitive impairment (Nordberg 2007), suggesting that the pathogenesis of AD starts years before clinical symptoms appear.

The progression of the involvement of brain regions in AD follows a fairly constant pattern, from the entorhinal cortex through the hippocampus and isocortex, finally extending into the neocortex. A variable degree of cortical atrophy with widening of the cerebral sulci and ventricles can also be detected in macroscopic examination of the brain of AD patients (Kumar et al. 2007). Typical brain imaging also shows decreased glucose consumption and increased binding of markers detecting A $\beta$  in AD (Herholz et al. 2007).

Vascular brain pathology includes diffuse lesions such as microinfarcts and lacunes often involving subcortical and critical brain areas, arterial territorial infarcts, white matter lesions, hippocampal sclerosis, and multi-infarct encephalopathy with post-ischemic lesions. Therefore, the pathogenesis of “VaD” is considered multifactorial, and typical lesions may result from systemic, cardiac or local large or small vessel disease (Jellinger 2008). Vascular lesions affect neuronal networks involved in memory and other cognitive functions leading to the clinical picture of memory disorder. Vascular lesions in mixed dementia and pure VaD related to microangiopathies differ from each other, suggesting different pathologies (Jellinger 2008). In addition, pure VaD is more often associated with large infarcts, while mild AD and small vessel disease are more often detected in the same patients and known to act synergistically (Jellinger and Attems 2005).

Initially thought to be uncommon, DLB is now considered as the second most common type of degenerative dementia. Most patients with DLB also show AD pathology, including amyloid plaques and neurofibrillary tangles. However, they also have unique pathological features not present in most AD patients: Lewy neurites representing neuritic pathology are suggested as the most likely link with clinical symptoms, and intraneuronal Lewy bodies containing fibrils, which are mainly comprised of an aggregated and insoluble form of  $\alpha$ -synuclein. Most patients with DLB do not have a genetic mutation in the  $\alpha$ -synuclein gene, and the reason for its pathological aggregation is not clear, since  $\alpha$ -synuclein is known as a normal synaptic protein implicated in vesicle production. Lewy bodies are detected by

ubiquitin or  $\alpha$ -synuclein immunohistochemistry in the brainstem, limbic system and neocortex (McKeith et al. 2004).

Close pathological (and clinical) similarities are found between DLB and PDD. Although autopsy studies have shown heterogeneity in terms of the distribution and density of Lewy bodies in DLB and PDD patients, there are no definite pathological criteria separating them from each other or from Parkinson's disease without dementia. In practice, the onset of dementia within 12 months of parkinsonism is considered as DLB, and later than 1 year as PDD (McKeith et al. 2004).

Frontotemporal lobar degeneration includes several pathological processes and clinical syndromes, in which circumscribed degeneration of prefrontal and anterior temporal lobes is detected. The distribution of atrophy determines the clinical syndromes of FTD (the most common form), progressive nonfluent aphasia and semantic dementia, in all of which microvacuolation of upper cortical layers and gliosis of the cortex and subcortical white matter may be detected. Sometimes, especially in FTD (but nevertheless only in less than half of FTD patients), microtubule-associated protein tau-based pathology (tau-reactive intraneuronal inclusions referred to Pick's bodies or tau-reactive neurofibrillary tangles in neurons referred as Pick-like bodies) is also present. In 10–30% of patients with a positive family history (representing around half of FTD patients), mutations in the tau gene are demonstrated, although other more common mutations in familial forms of FTD have also been demonstrated (Neary et al. 2005).

In addition to AD and frontotemporal lobar degenerations (mainly FTD), neurodegeneration accompanied by the deposition of tau aggregates is observed in progressive supranuclear palsy (with a prevalence of 1–2/100 000) and corticobasal degeneration (with an unknown prevalence, considered as very rare), which can also lead to dementia. P-tau deposits can be observed either in neurons (manifested as neurofibrillary tangles in AD and Pick's bodies in FTD) or in glial cells (in progressive supranuclear palsy and corticobasal degeneration). In the familial forms of these diseases, more than 40 different mutations associated with inappropriate formation of tau aggregates have been demonstrated (Tsuboi 2006).

### *2.1.3 Clinical picture and diagnosis*

The clinical picture and prognosis of dementia vary with respect to the underlying disease. In most cases, the clinical picture of dementia is characterized by progressive deterioration and interference with daily activities, eventually leading to the loss of independence and need for care. The usual survival time following diagnosis ranges from 5 to 10 years (Kester and Scheltens 2009).

The clinical criteria for AD include an insidious onset and progressive impairment of cognitive functions (McKhann et al. 1984, Dubois et al. 2007, McKhann et al. 2011). Impairment of episodic, i.e. working memory, which can be tested with neuropsychological tests such as Digit Span (Toepper et al. 2008), is typically the first symptom of AD. Later, memory problems are accompanied by impairment of other cognitive domains. In the presence of additional cerebrovascular damage common in older patients, the clinical presentation is usually slightly different, including other symptoms such as confusion, depression and delusions more often than early onset AD (Kester and Scheltens 2009).

The most common VaD is its subcortical form, referred to as subcortical ischemic vascular disease, which is characterized by the impairment of executive functions, lesser impairment of episodic memory than in AD and other diverse neurologic symptoms such as early onset urinary incontinence, which is usually only present in the late phase of AD. Cognitive deficits after a post-ischemic brain lesion depend on the size and location of the lesion and may also be abrupt. Consecutive vascular lesions cause a stepwise or fluctuating course, which is often also characterized by focal neurologic deficits, such as hemiparesis, sensory loss including visual field deficits, and/or extrapyramidal symptoms (Erkinjuntti 1994, Zanni and Wick 2007, Kester and Scheltens 2009).

The core clinical features of DLB are fluctuating cognitive impairment (over minutes to days) with shifting degrees of attention and alertness, parkinsonism (especially postural instability), and recurrent visual hallucinations and other psychiatric manifestations. Concomitant AD pathology in DLB modifies the clinical presentation, with a lower rate of visual hallucinations and parkinsonism, making it more difficult to differentiate clinically. In general, DLB patients have better verbal memory but worse visuospatial performance than

AD patients. However, the symptoms of DLB and PDD are similar. Disease progression and survival in DLB are comparable to or slightly worse than in AD (McKeith et al. 2004).

FTD is characterized by abnormal behaviour, including changes in affect and a lack of concern and appropriate social emotions, which help to distinguish it from AD and VaD. Other typical features include repetitive, stereotypic behaviours and changes in eating habits, altered responses to sensory stimuli and impairment of executive function, while memory, elementary visual perception and spatial and lingual skills are often well preserved. Non-fluent progressive aphasia is mainly characterized by impairment of expressive language, in which patients have difficulties in speech production, while other cognitive domains are usually well preserved. In semantic dementia, the ability of patients to name and understand words and to recognize objects is impaired (Neary et al. 2005). Considering the other disorders showing tau-based pathologies, progressive supranuclear palsy is most often presented by asymmetric akinetic-rigid syndrome, difficulties in moving the eyes downwards and impairments especially in planning and executive functioning (Stamelou et al. 2010). Furthermore, corticobasal degeneration is characteristic of parkinsonism, which is most often asymmetric, e.g. affecting only one arm, while cognitive symptoms are often similar to those in supranuclear palsy (Wadia and Lang 2007).

Cognitive screening tests, such as Mini-Mental State Examination (MMSE) (Folstein et al. 1983), Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Chandler et al. 2005), the 7 Minute Screen (Solomon et al. 1998) and the Clinical Dementia Rating (Berg 1984), may be useful in identifying individuals with a need for more accurate clinical examination in early diagnostics. Comparable tests have also been developed for telephone screening that have been used in several epidemiological studies (Brandt et al. 1988, Gatz et al. 1995). However, dementia can only be diagnosed on the basis of a thorough patient examination and careful history taken from both the patient and an informant. Clinical examination includes general physical, neurological and cognitive examination, and other available investigations including laboratory tests, cerebrospinal fluid examination and brain imaging. Laboratory tests are used to reveal any co-morbidities or risk factors for dementia, or the reason for delirium, which is an important cause of symptoms mimicking dementia.

Nowadays, neuroimaging is the most important ancillary investigation. Computed tomography (CT) can be used to exclude other potentially treatable illnesses, whereas the use

of magnetic resonance imaging (MRI) increases the specificity of the clinical diagnosis. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) may be useful in the case of an otherwise uncertain diagnosis, and should not be used as the only imaging measures (Waldemar et al. 2007). Determination of CFS biomarkers such as total tau, p-Tau and A $\beta$ 42 may help to disentangle AD from healthy controls and from other dementias, and may be helpful in the case of incipient AD and in differential diagnostics (Waldemar et al. 2007).

### *2.1.4 Risk and protective factors*

Although cognitive impairment can be temporarily relieved by using dementia medications, the main role of pharmacotherapy is in the symptomatic treatment of dementia. Since the beneficial effects of medication can only be considered as modest (Kester and Scheltens 2009), research on dementia should also focus on protective and risk factors. So far, the determinants of memory impairment in old age are still largely unknown.

The role of age as the most consistent risk factor for dementia (Kester and Scheltens 2009, Qiu et al. 2009) probably reflects the cumulative effect of different risk and protective factors during life. It is reasonable that the various forms of brain damage such as vascular lesions and increasing amyloid formation finally leading to clinical symptoms and memory impairment are due to complex interactions of genetic, environmental and psychosocial factors already present prenatally, in childhood or in later life.

#### *2.1.4.1 Genetic and environmental contribution*

The higher concordance rate of MZ (monozygotic) versus DZ (dizygotic) twins confirms the contribution of a substantial genetic component in cognitive functioning (Brandt et al. 1993, McGue and Christensen 2001, McGue and Christensen 2002), AD (Breitner et al. 1995, R ih a et al. 1996, Gatz et al. 1997, Bergem et al. 1997, Pedersen et al. 2004, Gatz et al. 2006a), VaD (Bergem et al. 1997) and dementia as a whole (Gatz et al. 1997, Gatz et al. 2006a). Whether hereditary effects are a major causal component remains unclear, as

probandwise MZ correlations have ranged between 0.21 (Breitner et al. 1995) and 0.83 (Bergem et al. 1997). At minimum, there is a significant set of environmental factors affecting memory impairment and dementia. Whether these factors are unique to each co-twin or some of them are also shared by both co-twins remains unclear, since the correlations within DZ twins were found to be either more (Breitner et al. 1995, Bergem et al. 1997, McGue and Christensen 2002, Gatz et al. 2006a) or less than half of that within MZ twins (Räihä et al. 1996, Gatz et al. 1997, Pedersen et al. 2004). In addition, the heritability of cognitive functioning has been found to decrease as a function of age (0.81 for a mean age of 65 and 0.62 for a mean age of 80 years) (Lee et al. 2010), and the role of environmental risk factors is also greater for later than earlier-onset AD (Silverman et al. 2005).

Inheritance of the Apoε4 allele, associated with at least 30% of sporadic AD cases, is the only well-established genetic risk factor (Blennow et al. 2006, Kumar et al. 2007). The pathological mechanisms behind this predisposition may be due to its less effective performance in the reusing of membrane lipids and neuronal repair compared to alternative APOε4 alleles or the promoting effect on Aβ fibrillation and plaque formation in the brain (Blennow et al. 2006). Having a higher number of APOε4 alleles has been found to increase the risk for AD in both sexes, but doubly in men (Qiu et al. 2004), and to decrease the age of disease onset (Blennow et al. 2006).

In addition to the APOε4 gene on chromosome 19 and genes associated with familial forms, several genes or genetic loci situated in nearly every chromosome, most of which are involved in Aβ metabolism, have been associated with AD (Blennow et al. 2006). The first genome-wide scans assessing the genetic predisposition to late-onset AD demonstrated three significant single nucleotide polymorphisms (SNPs) that were attributed to APOε4 (Heinzen et al. 2010), CLU and PICALM genes (Harold et al. 2009). Later meta-analysis of four genome-wide scans demonstrated seven more SNPs (CR1, BIN1, CD33, CD2AP, EPHA1, ABCA7 and MS4A genes) associated with AD (Hollingworth et al. 2011). Several of these genes are known to have putative functions in the immune system or are involved in processes in the cell membrane or in lipid metabolism. In the first copy number variation (CNV) scan of AD, nothing significant was found (Heinzen et al. 2010). However, since a strong association between several CNVs and mental retardation were demonstrated in another study, and many of the CNVs associated with mental retardation, autism and schizophrenia contain genes involved in neurotransmission and synapse formation and



maintenance, they may also play a role in the development of dementia (Hehir-Kwa et al. 2010).

#### *2.1.4.2 Vascular pathway hypothesis*

Several multidisciplinary studies have demonstrated that vascular and metabolic risk factors are associated not only with VaD but also with AD. This is in concordance with the finding that microvascular alterations also play a crucial role in AD (Brayne et al. 2001, Henry-Feugeas 2008), and vascular lesions in AD are very similar to those seen in “pure” VaD. In contrast, the pattern of vascular lesions in mixed dementia is different, suggesting other pathological mechanisms (Jellinger and Attems 2007).

The potentially predisposing effect of a high body mass index (BMI) on dementia has been emphasized, because both overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) and obesity (BMI  $> 30$  kg/m<sup>2</sup>), affecting more than 60% of American (Wyatt et al. 2006) and more than 50% of European adults (Hyde 2008), have reached epidemic proportions worldwide. Indeed, several longitudinal studies with a follow-up ranging from an average of 21 (Kivipelto et al. 2005) to 36 years (Whitmer et al. 2007, Sabia et al. 2009) and containing at least 1449 (Kivipelto et al. 2005) or even 7402 (Rosengren et al. 2005) subjects, have concentrated on this question. Some of them have established a clear association between both midlife overweight and obesity and lower cognitive performance (Sabia et al. 2009) or dementia (Rosengren et al. 2005, Whitmer et al. 2007), whereas others have found that only obesity and not overweight correlated with dementia (Kivipelto et al. 2005), obesity only increased the risk for AD in women with a waist circumference in the highest quintile, but not in men (Beydoun et al. 2008), or no correlation has been found (Stewart et al. 2005). The effect of a high BMI on cognitive decline in old age may be partly mediated by metabolic disorders ensuing from a high BMI, which may partly explain the diverging results of these studies and their inability to show a clear association between different levels of high BMI or between sexes.

Studies concerning the association between midlife weight change and cognition in old age are rare. An increase in the BMI corresponding to 4.9 kg/m<sup>2</sup> in men and 6.7 kg/m<sup>2</sup> in women has been found to correlate with a lower performance in one of three cognitive tests (Sabia et al. 2009). In addition, the risk for AD was found to increase up to 5-fold among 30- to 50-

year-old men with a 4.7–27.3% weight gain within 5 years, whereas weight loss had no significant effect among them (Beydoun et al. 2008). However, women with a 0.6–6.1% weight loss within 5 years at the age of 30–45 years had almost a doubled risk for AD compared to women with a weight gain of up to 5.3%, indicating an even more harmful effect of weight loss than weight gain among them (Beydoun et al. 2008).

A significant association between midlife diabetes and old age MCI (Roberts et al. 2008) or dementia has been found (Schneider–Beeri et al. 2004, Xu et al. 2009), but not in all follow-up studies (Curb et al. 1999). Moreover, the findings of a Swedish twin study suggest that this association cannot be accounted for by unmeasured genetic or childhood environmental factors (Xu et al. 2009). Although the findings of epidemiological studies concerning the association between altered insulin secretion and poorer cognitive performance later in life are more consistent (Kuusisto et al. 1997, Young et al. 2006, Rönnemaa et al. 2008), the results concerning hyperglycemia, the major diagnostic manifestation of diabetes, are inconsistent (Curb et al. 1999, Chiang et al. 2007, Dik et al. 2007).

Indicators of atherosclerosis, i.e. cardiovascular disease (Newman et al. 2005), vessel wall thickness (Hofman et al. 1997, Altamura et al. 2007), plaques of the carotid arteries (Hofman et al. 1997, van Oijen et al. 2007), peripheral arterial disease (Newman et al. 2005), the ankle-to-brachial index as an indicator of peripheral arterial disease (Hofman et al. 1997, Laurin et al. 2007), coronary heart disease (Beeri et al. 2006, Singh-Manoux et al. 2008) and heart failure (Qiu et al. 2006), have been associated with dementia, AD or poor cognitive performance. In addition, the frequency of dementia and its major subtypes has been found to increase with the degree or duration of atherosclerosis (Hofman et al. 1997, Newman et al. 2005, Singh-Manoux et al. 2008). However, only one study has used the parameter as already measured in midlife (Singh-Manoux et al. 2008).

In the elderly, cross-sectional studies have shown an inverse association between blood pressure (BP) and dementia (Qiu et al. 2005). However, the findings of longitudinal studies have been inconsistent, since an association has been demonstrated between both high (Skoog et al. 1996, Qiu et al. 2003) and low (Morris et al. 2001, Qiu et al. 2003, Verghese et al. 2003, Petitti et al. 2005, Ruitenberg et al. 2005) BP in old age and dementia. The inconsistency of these results is largely due to age differences at the time of measurement and

the different durations of follow-up periods (Qiu et al. 2005). Indeed, untreated BP in midlife has been associated more often with an increased risk for impaired cognition (Qiu et al. 2005), AD (Launer et al. 2000, Kivipelto et al. 2001) and dementia (Launer et al. 2000), although contradictory findings also exist (Rosengren et al. 2005, Qiu et al. 2005).

In the elderly, low levels of high-density lipoprotein (HDL) were more commonly detected in women with AD than without (Vanhanen et al. 2006), whereas neither serum cholesterol (Chiang et al. 2007) nor triglycerides increased the risk for dementia (Chiang et al. 2007, Dik et al. 2007). In middle-aged subjects, some studies have found an association between high cholesterol levels and AD and dementia in later life (Notkola et al. 1998, Kivipelto et al. 2001, Whitmer et al. 2005), whereas two other studies failed to detect any association between hypercholesterolemia and AD (Tan et al. 2003) or hospitalization related to dementia (Rosengren et al. 2005).

#### *2.1.4.3 Nutritional factors, alcohol use, smoking and physical activity*

Many nutritional compounds may have an independent effect on brain and cognitive functions. For instance, diet antioxidants may reduce inflammation and thus reduce the risk of dementia (Middleton and Yaffe 2009). Indeed, a higher concentration of serum inflammatory markers, such as C-reactive protein, already in midlife has been found to associate with an increased risk of dementia (Qiu et al. 2009), while a Mediterranean diet and a higher intake of fruits, vegetables and antioxidant vitamins such as E and C have been shown to associate with a reduced risk of cognitive decline, AD and dementia. Folate, homocysteine-related vitamins, especially B9 and B12, fish consumption (Luchsinger et al. 2007, Gillette-Guyonnet et al. 2007) and the long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) (Qiu, et al. 2009) have also shown favourable associations. Conversely, a high intake of saturated and transunsaturated fats associated with an increased risk of AD (Luchsinger et al. 2007, Gillette-Guyonnet et al. 2007). However, associations between nutritional factors and BMI, metabolism and cardiovascular health can also represent a causal link between nutritive factors and cognitive performance.

Coffee drinking has a beneficial influence on diseases associated with the risk of dementia such as cardiovascular disease (Kleemola et al. 2000), hypertension (Robertson et al. 1984,

Umamura et al. 2006) and T2DM (van Dam and Feskens 2002, Tuomilehto et al. 2004, Carlsson et al. 2004). Since many biologically active substances in coffee include antioxidative compounds, coffee may also have an independent effect on memory disorders. Besides the antiatherosclerotic and anti-inflammatory mechanisms of coffee, caffeine may affect cognition by blocking adenosine A2a receptors (Arendash et al. 2006, Dall'Igna et al. 2007) and increasing the intracellular calcium concentration in brain neurons (Smith et al. 2005).

However, the results of epidemiological studies concerning coffee consumption and memory impairment are inconsistent. A case-control study demonstrated that AD patients consumed less coffee preceding their diagnosis than healthy controls (Maia and de Mendonca 2002), and two of four cross-sectional studies revealed that current coffee consumption enhanced cognitive performance among subjects under age of 50 years (Jarvis 1993) and at the age of 70 years (Corley et al. 2010), whereas one showed that only life-time coffee consumption had an enhancing effect among older women, but not in men (Johnson-Kozlow et al. 2002), and fourth did not find any association (Kyle et al. 2010). Greater caffeine consumption was also associated with lower white matter lesion/cranial volume ratios in a sample of elderly French women, but not in men (Ritchie et al. 2010). Five prospective studies found that coffee consumption protected against AD (Lindsay et al. 2002, Eskelinen et al. 2009) and cognitive decline (van Gelder et al. 2007, Ritchie et al. 2007, Santos et al. 2010a), whereas one concluded that coffee intake did not counteract cognitive decline at baseline (Hameleers et al. 2000) or during follow-up among subjects whose average age was, however, less than 52 years (van Boxtel et al. 2003).

The effect of alcohol drinking on cognition is controversial and apparently depends on the type of drink and amount consumed, since most studies have found a beneficial effect of moderate wine consumption but not other alcoholic beverages (Luchsinger et al. 2007). This may be due to antioxidants in wine, which are not present in most other alcohol-containing drinks, or may reflect the effect of confounding variables associated with wine drinking. However, even a single episode of binge drinking has been found to damage brain regions associated with AD (Obernier et al. 2002), and alterations in gene expression of these regions were detected even after 8 weeks of binge drinking exposure in rodents (McBride et al. 2010). Indeed, binge alcohol drinking in midlife (in subjects of this study population) (Järvenpää et al. 2005) and in old age (Luchsinger et al. 2007) are associated with an

increased risk of AD. Moreover, in the population of this study, both abstainers (but only without an APOε4 allele) and women drinking more than 7 alcohol drinks and men drinking more than 14 alcohol drinks per week were found to have an increased risk of cognitive impairment (Virta et al. 2010).

In addition to exposures in adulthood, nutritional conditions during childhood or prenatally may have long-standing influences on health. A recent review examining nutritional deficiencies in preschool children concluded that brain regions critical for learning and cognition do not reach maturation during this period, and nutritional deficiencies will delay these performances for a long time (Yehuda et al. 2006).

Variation in adult height within the population is mainly due to genetic factors, but also reflects a set of environmental exposures present during pregnancy, childhood and adolescence (Silventoinen et al. 2003a). Thus, several epidemiological studies have used height measurement as an indicator of the childhood living environment, and an association has been demonstrated between short adult height and poor cognitive performance in old age (Abbott et al. 1998, Jeong et al. 2005) or specific dementing diseases, mainly AD (Abbott et al. 1998, Petot et al. 2007) and vascular dementia (VaD) (Beeri et al. 2005), or dementia as a whole (Beeri et al. 2005, Gatz et al. 2006b). Similarly, early tooth loss in adulthood indicating poorer childhood living conditions has been associated with AD (Kondo et al. 1994). However, on the basis of these studies, it cannot be stated whether these associations are due to a shared genetic or environmental predisposition of short people. In addition, this predisposition may increase the vulnerability to genetic or later life environmental factors leading memory impairment.

A current review stated that perinatal conditions, early-life brain development, growth in height and socioeconomic conditions are each associated with an increased risk of AD (Borenstein et al. 2006). Although they are closely connected with nutritional conditions, these associations may also reflect the effect of psychosocial factors during the growth period.

Current smoking is known to increase the risk of dementia, especially AD, but there is lesser evidence of the effect of former smoking (Peters et al. 2008). Participation in leisure-time physical activities is associated with a reduced risk of AD (Lindsay et al. 2002, Scarmeas et

al. 2009) and dementia (Fratiglioni et al. 2004, Chang et al. 2010), whereas job-associated higher physical activity has been associated with lower cognitive performance (Potter et al. 2008) and dementia (Smyth et al. 2004) in older ages, which may reflect both the protective effect of a higher education or the harmful effect of unbalanced physical strain, which may be associated with physically demanding jobs. Furthermore, leisure-time physical activity may indicate more social contacts and an active lifestyle.

#### *2.1.4.4 Psychological and social factors*

Sex differences in VaD have not been demonstrated, although the prevalence of both AD and dementia as a whole has been found to be higher in women than in men (Andersen et al. 1999, Lobo et al. 2000). However, this observation is not consistent in different populations (Berr et al. 2005). Instead, there is a clear association between a lower educational level, AD and dementia (Launer et al. 1999, Qiu et al. 2001, Lindsay et al. 2002, McDowell et al. 2007, Ngandu et al. 2007), which cannot be explained by a more unhealthy lifestyle of lesser-educated subjects or a higher incidence of cardiovascular diseases among them (Ngandu et al. 2007). Neither, though, is education known to be an indicator of socioeconomic status (SES), its effect on cognitive performance is not mediated by adult SES (Evans et al. 1997, Karp et al. 2004).

Intellectually demanding jobs are associated with better cognitive performance in old age, independently of education. The existence of significant associations among DZ but not MZ twins suggests that this relationship may be mediated by genetic factors (Potter et al. 2006). Interestingly, individuals with a lower intellectual aptitude were found to have a stronger positive association between work and cognitive performance in later life, suggesting that they benefit most from intellectually demanding work (Potter et al. 2008). The effect of education on cognition in old age probably also reflects the impact of intellectual duties throughout working life.

The lack of a consistent correlation between the degree of brain pathology and clinical symptoms has led to the proposal of the theory of cognitive reserve (Stern 2006, Stern 2009). According to this hypothesis, there are individual differences in the cognitive reserve against brain pathology and age-related changes, due to the lesser susceptibility of more actively used

brain networks to disruption and/or the existence of alternative pathways that are able to compensate for damaged connections. Thus, persons with a higher educational level are thought to have a greater brain reserve. Whether education creates an additional reserve against the clinical manifestation of dementia, or is a result of a greater cognitive reserve, or both, is not known (Ngandu et al. 2007), although some studies have demonstrated an association between mental ability test results even at school age (Whalley et al. 2000), early adulthood autobiographies (Snowdon et al. 1996, Riley et al. 2005), the number of siblings and area of residence before the age of 18 years (Moceri et al. 2000) and dementia, suggesting that a poor childhood environment may prevent the brain from reaching complete maturation and reserve. Indeed, brain areas showing the earliest signs of AD are those taking the longest to mature (Braak and Braak 1991).

Both animal and epidemiological studies have shown that an active and socially integrated lifestyle in old age protects against AD and dementia, regardless of the educational level (Fratiglioni et al. 2004). Both physical and non-physical activities, such as dancing, travelling, gardening and knitting, have all shown beneficial effects. Whether they reduce the lifetime risk of dementia or merely postpone the onset of disease is unclear. However, mid-life political, mental and socio-cultural activities have also been demonstrated to associate with better cognitive performance more than 20 years later (Kareholt et al. 2011). Conversely, being single, widowed, never married or living alone were found to increase the risk of AD and dementia. In addition, depression must be taken into account as a differential diagnosis for memory disorder, but is also known to be a risk factor for dementia (Fratiglioni et al. 2004).

## 2.2 Coffee

### 2.2.1 Composition

The two main commercially cultivated species of the genus *Coffea* are *Coffea arabica* and *Coffea canephora* var. *robusta*, both of which cover a number of varieties. The coffee drink is made from beans, which are cultivated, separated from the whole fruit, dried, stored, shipped, possibly decaffeinated or otherwise “improved”, roasted, ground and packaged. In each of these stages, biologically active substances of coffee beans may be transformed, especially during the roasting process in which thermal transformation is likely to occur. At the same time, some new compounds are yielded.

Roasted coffee contains about 30% carbohydrates and 10% proteins. Most of the lipids are in the form of coffee oil, representing around 12% of Arabica and 4.5% of Robusta coffee composition; 79% of this oil consists of triglycerides, 17% terpene esters and 4% sterols, free terpenes, tocopherols and unknown substances (Spiller 1998).

The main terpene molecules present in coffee are diterpenes cafestol and kahweol. They are only present in small amounts in the fat of the coffee beans, but are responsible for the hypercholesterolemic effect of unfiltered coffee. Since they are largely trapped by the use of paper filter during coffee preparation, they are not substantially present in filtered coffee. Thus, the type (filtered versus boiled) of consumed coffee is an important issue that must be taken into account in epidemiological studies (Spiller 1998).

In addition, coffee contains vitamins, some inorganic compounds and alkaloids, mainly caffeine, which plays a role in the defence system of the coffee seed by acting as a selective antifungal phytotoxin and a chemosterilant towards certain insects (Spiller 1998). Caffeine is also the most studied component of coffee and responsible for coffee addiction. Its psychoactive effects include increased mental alertness, faster information processing, wakefulness and a delay in the need of sleep (Harland 2000). Since caffeine also has an antioxidative activity, it may be responsible, at least partly, for several positive health effects of coffee.



In addition to caffeine, coffee also contains other antioxidants, and the removal of caffeine from espresso coffee was found to decrease the antioxidant capacity by only 25–30% (Pellegrini et al. 2003). The antioxidant activity of coffee is known to decrease with light, and increase with stronger roasting, although never exceeding that observed in green coffee without any roasting procedures. This is probably due to the destruction of protective polyphenolic compounds during light roasting and the formation of other highly protective antioxidant compounds such as Maillard reaction products or pyrolysis products during further processing (Daglia et al. 2000).

### *2.2.2 Consumption*

In 2007, Finnish consumed an average of 12.0 kg coffee (weight in green bean equivalent, 1 kg of green coffee beans = 0.84 kg of roasted coffee) per inhabitant. According to the World Resources Institute, the most recent figures for yearly coffee consumption per capita did not reach this level in any other population. Only five other nations consumed more than 8 kg: Norwegians (9.9), Icelanders (9.0), Danish (8.7), Dutch (8.4) and Swedish (8.2). The latest yearly coffee consumption figure for an average European was 4.1 kg in 2007, while an average inhabitant in North America consumed 4.4 kg in the same year. Compared to the mean consumption of 4.1 kg per inhabitant in high income countries, an average inhabitant in low and middle income countries consumed only 0.2 kg and 0.8 kg in 2007.

Since 1975, global coffee consumption has varied slightly between years, the highest value being 14.5 kg in 1976 in Finland (Figure 2). Comparable consumption took place in Sweden (14.2 kg) in the same year. Thus, Nordic countries can be considered as the heaviest coffee consumers in the World. In Finland, the yearly coffee consumption has remained stable, ranging from 7.9 kg (1995) to 14.5 kg (1976). Given the ample supply of coffee and its central role in Finnish society, virtually all Finns can be expected to be exposed to coffee drinking.

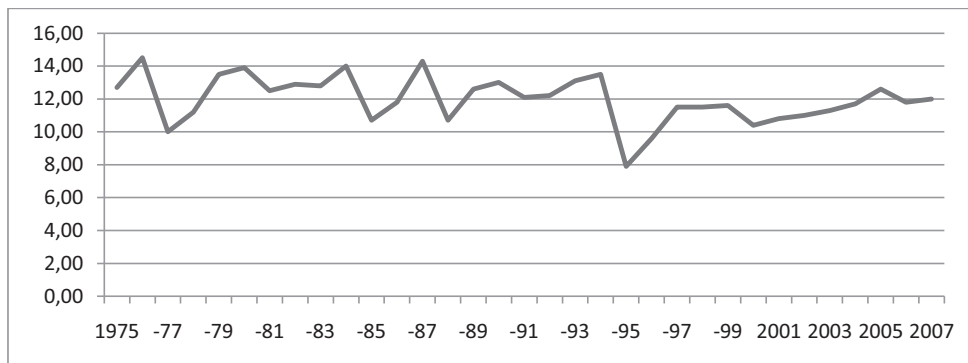


Figure 2. Finnish yearly coffee consumption (kg of green beans) per inhabitant according to World Resources Institute (2007).

In Finland, filtered coffee started to replace the consumption of boiled coffee in the 1960s, although boiled coffee was earlier the most frequently drunk coffee type. In a national survey of 5700 Finns aged 25–64 years, 69% of subjects drank filtered coffee, 24% drank boiled coffee, whereas those drinking both filtered and boiled coffee represented only 0.6% of the study population in 1987. Boiled coffee drinkers were older, had a higher saturated fat intake calculated on the basis of milk-fat consumption and the amount of fat spread used on bread, and had a higher serum total cholesterol level (Pietinen et al. 1990). Indeed, other studies have also demonstrated a clear association between boiled coffee drinking and higher serum cholesterol concentrations, whereas filtered coffee drinking has shown a substantially weaker or no association (Kokjohn et al. 1993).

### 2.2.3 Impact on human health

Taken into consideration the extensive consumption of coffee and its central role in Finnish society, the health effects of habitual (“chronic”) coffee consumption are relevant to public health. The short-term, acute effects of coffee drinking or caffeine administration are usually based on other biological mechanisms and may thus be reversed (Geleijnse 2008).

Since coffee is the main source of caffeine in most populations, it is difficult to distinguish the impact of caffeine and coffee on human health. Comparison of caffeinated and decaffeinated coffee consumers can partly overcome this problem. However, there are also

other sources of caffeine such as tea, chocolate, colas and energy drinks (Cornelis and El-Sohemy 2007). In addition, since there is a common genetic pathway affecting tobacco, alcohol and coffee use (Swan et al. 1996, Hettema et al. 1999), and coffee is also associated with other health and socioeconomic variables in some populations, studying the independent effect of coffee on various health outcomes calls for relevant adjustments. For instance, higher coffee consumption was associated with male sex, a lower level of education, higher BMI, smoking, alcohol drinking, lesser physical activity and a less favourable diet in a Dutch sample (van Dam and Feskens 2002). In Finland, greater coffee consumption associates at least with female gender, a lower level of education, higher BMI and smoking (Laitala et al. 2009). Taking into account the various roles of coffee in societies, these associations vary among populations.

A dose-response protective effect of at least 4 daily coffee cups (van Dam 2008) on type 2 diabetes (T2DM) has consistently been demonstrated across subgroups of diabetes risk factors and within different populations, including Finns (Hu et al. 2006). However coffee consumption was not associated with T2DM in all Finnish study samples (Reunanen et al. 2003), or the protective effect was significant only for higher amounts ( $\geq 7$  daily cups) of coffee consumption (Carlsson et al. 2004). Meta-analysis of 20 cohort studies concluded that drinking 3 to 4 daily coffee cups reduced the risk for T2DM by approximately 25% compared to those drinking 2 cups or less, and tea and decaffeinated coffee consumption also showed a comparable protective effect (Huxley et al. 2009). Indeed, in addition to caffeine, several other compounds of coffee including chlorogenic acids, quinides, magnesium and lignans have improved glucose metabolism in animal studies (van Dam 2006). Moreover, a recent study suggested that decaffeinated coffee may have an even better effect on glycemic control in diabetic individuals compared to caffeine-containing coffee (van Dam 2008).

Experimental data indicate that tolerance of the acute raise in BP after caffeine administration develops rapidly and heavy coffee drinkers are not likely to show a BP response after caffeine administration (Geleijnse 2008). Since caffeine had a greater increasing effect on BP than caffeinated coffee with intervention duration of at least 7 days, other components of coffee may reduce the BP-raising effect of caffeine (van Dam 2008). Indeed, prospective epidemiological studies suggest a lowering effect of 4 or more daily cups of coffee on BP (Geleijnse 2008). In addition, some prospective studies have shown a decreased risk of coronary heart disease in moderate coffee consumers (Cornelis and El-Sohemy 2007).

Although some studies suggest that coffee drinking may trigger a myocardial infarction by sympathetic nervous activation in persons with infrequent coffee consumption, results from prospective cohort studies show that long-term coffee consumption is not associated with an increased risk of coronary heart disease (van Dam 2008). Neither is there consistent evidence of any increase in the risk of stroke among coffee consumers (van Dam 2008).

Some individuals may be genetically more vulnerable to the cardiovascular effects of coffee and caffeine. For instance, there is large variability in the activity of P450 1A2 (CYP1A2), an enzyme responsible for 95% of caffeine metabolism, and coffee intake was found to be associated with an increased risk of nonfatal myocardial infarction only among carriers of the slower variant of this enzyme (Cornelis et al. 2006).

Coffee consumption has been associated with several types of cancers, but many of these findings cannot be confirmed in other studies, especially in large prospective cohort studies. The overall evidence does not support a substantial relationship between coffee and cancer, with the exception of an inverse association between coffee and liver cancer and maternal coffee consumption and childhood leukemia. Evidence suggests that coffee is also associated with a lower risk of liver cirrhosis, and high coffee or caffeine consumption during pregnancy with a lower birth weight, as well as a higher risk of miscarriage and stillbirth (van Dam 2008). Evidence also suggests that coffee drinking reduces the risk for Parkinson's disease (Logroscino 2005) and AD (see 2.1.4.3).

## *2.3 Twin modelling and heritability*

### *2.3.1 Inheritance and sources of genetic variation*

Both genetic and environmental influences affect human behaviour. Using a quantitative genetic approach, phenotypic variation, i.e. the amount by which individuals differ from each other in relation to a certain phenotype, may be attributed to genetic and environmental causes:

$$\text{Var (P)} = \text{Var (G)} + \text{Var (E)}$$

Genetic material is stored in cell nuclei, each of which contains 23 chromosome pairs (2n). One of the homologues of each chromosome is inherited from each of the parents, except for gametes, which are haploids (1n), and mitochondria, which contain maternal DNA. The haploid human genome comprises approximately 3 billion DNA base pairs, with around 20 000–25 000 protein-coding genes representing only 1% of the total genome sequence. An additional, but still unknown portion is involved in the regulation of gene expression (International Human Genome Sequencing Consortium 2004).

The 1000 Genomes Project established a total of 15 million SNPs, 1 million short insertions and deletions and 20 000 structural variants, including CNVs, by using the latest strategies for genome-wide sequencing. In addition, approximately 10 000–11 000 sites were demonstrated at which DNA sequence differences led to differences in protein sequences between any two human individuals. However, only a fraction of these coding variations are likely to have a significant functional impact, and most contributions to common variations in complex traits are likely to be regulatory in nature (1000 Genomes Project Consortium 2010).

Inheritance refers to the transmission of genetic information between generations through the reproductive cells, i.e. gametes, which is the basis of genetic variation between individuals. Two kinds of randomizing genetic reassortment during meiosis before the fusion of gametes at fertilization are responsible for genetic variance between offspring of the same parents, excluding MZ twins who develop from a single zygote and thus share the same genome. The random distribution of maternal and paternal homologous chromosomes between the

daughter cells at the first meiotic division represents the first type of reassortment. From this process alone, a human individual having 23 chromosome pairs could produce  $2^{23}$  ( $=8.4 \times 10^6$ ) genetically different gametes. However, chromosomal crossing-over, i.e. the exchange of parts of homologous chromosomes, increases the genetic variation. Genetic recombination refers to the formation of new combinations of alleles due to crossing-over (Alberts et al. 2002). Finally, the fusion of gametes in fertilization combines the genetic material of two individuals.

Each individual is estimated to carry approximately 50–100 variants previously implicated in inherited diseases. However, the types of disease for which variants are identified is biased, so that diseases of the nervous system are significantly under-represented (1000 Genomes Project Consortium 2010).

### *2.3.2 Heritability and its analysis*

The heritability of a certain trait is the proportion of total phenotypic variance that is attributable to variation in the total genetic value.  $H^2$  is termed broad-sense heritability and can be expressed as the ratio of genetic variance over total variance:

$$H^2 = V(G) / V(P)$$

Meanwhile,  $h^2$  is the proportion of total phenotypic variance that is attributable to variation only in additive genetic factors:

$$h^2 = V(A) / V(P)$$

Since individuals transmit only one copy of each gene to their descendants,  $h^2$  is the source of genetic variation between parents and offspring (dominant and other non-additive genetic effects that are based on the sharing of two copies do not contribute to their phenotypic resemblance). However, genetic variance in the population is due to both additive (additive effects of alleles in different loci), dominant (interactions between alleles at the same locus) and epistatic (interactions between alleles at different loci) genetic variances.

Heritability depends on time and the population, since both genetic and environmental variations are population specific. Genetic variance in a population depends on the segregation of relevant alleles, their frequencies and effects sizes, and mode of gene action, which can all differ across populations. Similarly, environmental exposures may vary in different populations. However, heritabilities of similar traits are often found to be remarkably similar between populations (Visscher et al. 2008).

Environmental exposures are often more similar among relatives than among non-related individuals. Thus, the use of family data may lead to overestimation of heritability, since shared environmental effects mimic the genetic resemblance of family members (i.e. common environmental and genetic factors are estimated together). Instead, the effect of the common environment can be separated from that due to genetic similarity by using quantitative genetic modelling of twin data or adoption, and by using measures of specific environments and specific genes.

### *2.3.3 Classic twin design*

Since heritability is a measurement of inheritance, its estimation requires data from relatives such as twins. In addition, a twin design can also be used to investigate environmental effects and factors affecting the trait in question. The classic twin design consists of both MZ and DZ twin pairs, both of which have been reared together, or separately in adoption studies. The classic twin design is based on an assumption that DZ twins share an average of 50% of their segregating genes similarly to other full siblings, whereas MZ twins share the same genome at the sequence level. Comparison of MZ and DZ concordances, i.e. the occurrence of the same trait in both members of a twin pair, or within pair correlations in the case of continuous traits, reveals whether genes play a role in the phenotype under study. A higher concordance or correlation of MZ compared to DZ twins can be taken as evidence of the influence of genetic factors.

Genetic resemblance between twins is divided into additive (A) and dominant (D) genetic effects reflecting the summed effect of alleles at different loci (A) and interaction effects

between alleles at the same locus, again summed over all relevant loci (D). The expected correlation of genetic effects is 1 within MZ twin pairs, whereas the expected correlation of A and D is 0.5 and 0.25 within DZ twin pairs. Thus, the presence of D instead of A reduces the expected phenotypic resemblance of DZ relative to MZ twins. Environmental effects are defined as common (C) and unique (E), whose correlations are 1 and 0 by definition within both MZ and DZ twin pairs. C is the sum of environmental factors similarly affecting both co-twins, making them more similar, such as the childhood family environment, whereas E represents non-shared environmental factors increasing the dissimilarity of twins, and is responsible for all dissimilarity in MZ twins. In many twin models, including the models of this study, E also includes measurement error.

Rough estimates of the relative contributions of various sources of variation to phenotypic variation can be calculated from simple mathematical equations (presuming that intraclass correlations of MZ and DZ twins are known), but this correlation-based method simply provides estimates. However, decomposing phenotypic variance into A, E and either D or C components at the same time by using linear structural equations (Neale and Cardon 1992) solved by computer allows the determination of confidence intervals, testing of the validity of modelling assumptions and provides information about the goodness-of-fit of the models. Disentangling the contributions of D and C requires data from twins reared apart, half-sibs or non-biological relatives reared together, and cannot thus be separated in most twin samples (Posthuma et al. 2003).

A univariate model can be used to explain the variation in the phenotype under study, which is treated as a dependent variable. Variance components are treated as latent and standardized independent variables, which are used to explain the phenotypic variance. Model evaluation is based on comparison of a simplified model with the model in which it is nested. Starting with either an ACE or ADE model, the significance of A, E and either C or D can be tested. Nonsignificant components can be omitted to seek the most parsimonious model (i.e. AE/CE/E). However, as the E component includes measurement error, it cannot be omitted.

Similarly to the partitioning of variation into its components, covariation between multiple phenotypic traits can be divided into genetic and environmental components under the aforementioned confines. The correlation between two traits, i.e. how much they are



influenced by the same genetic or environmental factors, can be performed with multivariate models, such as the bivariate Cholesky decomposition (Neale and Cardon 1992).

#### *2.3.4 Assumptions of classic twin modelling and potential concerns*

The correct estimation of variance and covariance components of the trait in question requires fulfilment of the assumptions of twin modelling, i.e. an equal effect of the environment in MZ and DZ twins, random mating and interactions between genes and the environment (GxE).

Twin modelling assumes no differences between the means within MZ and DZ twin pairs and an equal degree of environmental variation within them. Thus, differences between means and/or unequal variation restrict the performance of genetic models. Although differences in the means and/or equality of the environment (amount of variation) are not generally expected (Kaprio 2007), this can be tested in quantitative genetic modelling (see 4.3.2). On the contrary, potential differences in the similarity of the environment within MZ co-twins compared to DZ co-twins would not violate the principles of genetic modelling, since the greater similarity of MZ twins can be interpreted as a product of genetic factors and is thus correctly modelled as part of genetic variance.

Twin modelling assumes random mating of parents for the trait under study. Non-random mating refers to phenotypic correlation between spouses and occurs when mating within one's own social group is preferred due to environmental conditions (social homogamy), or when mate selection is based on a certain phenotype (assortative mating). Statistically, assortative mating in relation to phenotype, which is at least partly heritable, increases the apparent common environmental variation in twin studies (if assortative mating is ignored), since it increases the additive genetic correlation within DZ pairs to more than the value of 0.5 that is expected in twin models. In addition, it may also lead to greater passive GE correlation among offspring and greater additive genetic variation at the population level. Assortative mating is known to occur for traits such as height, BMI (Silventoinen et al.

2003b) and intelligence (Posthuma et al. 2003). However, social homogamy does not necessarily increase the genetic resemblance of family members.

GxE interaction means that the effects of genetic factors may be conditional on an individual's environment. The presence of unconsidered GxEs is a potential concern in twin modelling. If the modification variable represents E, a model without GxE results in overestimation of E. However, ignoring the effect of modification variable representing C will result in overestimation of the genetic effect. Taking account of all relevant environmental modification variables is virtually impossible, and testing of the GxE interaction if both genetic and environmental variables are latent usually suffers from a lack of power and is sensitive to non-normality in the trait (Purcell 2002). Indeed, rather than adjusting for multiple confounders, modelling of GxE interactions is useful in the study of specific environmental factors (see 2.3.5).

In addition to interaction between genes and the environment, there may be interactions between genes at different loci, i.e. epistatic genetic effects. However, genetic interactions are modelled as part of genetic effects and are not therefore likely to be a problem. When separating the genetic component into A and D, the interaction effect between closely linked loci, i.e. those that are inherited together, is modelled as part of A, whereas interactions between genes that are not linked are modelled as part of D.

Genotypic and environmental values can also be correlated in three ways. Passive GE correlation occurs when both genetic and environmental advantages are transmitted by parents, for instance musically gifted children may have the relevant equipment available without any individual effort, and is modelled as part of C. Active GE correlation is modelled as part of A and occurs when an individual selects an environment supporting the genotype, for instance musical individuals actively find their way to music groups. Reactive GE correlation, which is also modelled as part of A, refers to the effects of the reaction evoked by an individual's genotype, for instance when parents buy an instrument for musical children. Positive GE correlations lead to an increase in phenotypic variance at the population level (Jaffee and Price 2007).

Epigenetics refers to changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence. They can be induced by environmental stimuli (during

development or later) or may be formatted stochastically, for example during mitosis, when methylation or other epigenetic patterns are transmitted to daughter chromatids with a three times lower degree of fidelity than the DNA sequence. Depending on the underlying causes, they will be modelled as part of either genetic or environmental components. Contrary to family studies, twin-based epigenetic heritability is limited to a single generation and originates from partial epigenetic stability in somatic cells (Petronis 2010).

### *2.3.5 Gene-environment interaction analyses*

GxE is likely to be a common and an important source of variation for complex behavioural traits. By dividing the genetic component into a mean independent part and a part that is a linear function of the environment, one or more environmental modification variables can be incorporated in variance components of twin models. From the gene's point of view, the concept of the environment is relatively broad and includes the internal biochemical state and composition surrounding the gene. Having both G and E as measured variables provides the most power to detect GxE (Purcell 2002).

The most common incentive to perform GxE analyses is to determine whether measurable variables, such as age, height or physical activity, play a role in gene function, i.e. whether there is greater or lesser variation in certain phenotypes across these variables. For instance, physically active individuals often seem to be more similar in their BMI, whereas there is greater variation in BMI among sedentary people. In this case, GxE modelling has revealed that the genetic variation in BMI is reduced in physically active subjects, since significant GxE has been detected between genes affecting BMI (treated as a single latent variance component) and physical activity, which represents a measured environmental modification variable (Silventoinen et al. 2009).

Environmental moderator variables can affect both genetic and environmental variances of the trait in question in addition to the mean effect. The effect of both binary and continuous environmental modification variables can be tested. In the latter case, the most basic GxE interaction implies that genetic effects increase or decrease as a linear function of the moderator (while the effect of environmental factors goes conversely). However, if sufficient

data are available, a non-linear modification effect can also be considered, where the genetic effect may be attenuated at the extremes or within the moderator levels (Purcell 2002). The results of GxE analysis may be a key in beginning to understand the underlying biological mechanisms. For instance, the results of the aforementioned studies suggest that physical activity may modify the actions of the genes responsible for predisposition to obesity, which has been confirmed in studies on measured genes (Li et al. 2010).

### *3. Aims of the study*

This study aimed to determine the effect of midlife metabolic conditions and height on cognition in old age. In addition, the sources of inter-individual variation in coffee drinking in the Finnish population and whether coffee drinking has any effect on cognitive performance in old age were key interests of this study.

To address these issues, the specific aims were following (roman numerals refer to the original publications):

- To estimate the heritability of coffee consumption in various age groups of the Finnish population and to investigate whether age affects the relative contributions of genetic and environmental factors (I);
- To estimate the stability of coffee consumption and the relative influence of genetic and environmental factors on this stability (I);
- To investigate whether coffee drinking in middle age has an effect on cognitive performance in old age (II);
- To investigate whether and to what extent midlife BMI, weight change and associated metabolic conditions including diabetes, cardiovascular disease, hypertension and hypercholesterolemia influence cognitive performance in old age (III);
- To investigate whether there is evidence of a causal relationship between higher midlife BMI or metabolic conditions and poorer cognitive performance in old age (III);
- To explore whether midlife height is associated with cognitive performance in old age in two related Nordic populations with different childhood living conditions (IV);
- To analyse the contributions of genetic and environmental factors to cognitive performance in old age across height, and whether height affects the relative genetic or environmental contributions (IV).

## *4. Materials and methods*

### *4.1 Subjects*

#### *4.1.1 Finnish twins*

This study was based on the older cohort of the Finnish Twin Cohort Study (Kaprio and Koskenvuo 2002), consisting all Finnish same-sex twin pairs born before 1958 with both co-twins alive in 1975. Sampling was carried out from the Central Population Registry of Finland in 1974, and participants were contacted for the first time in 1975 by postal questionnaires. A total of three postal surveys of the entire cohort have been carried out (in 1975, 1981 and 1990), and in this study the first two of these were used, since they contain information on the mid-life health and socio-economic factors of the respondents.

In 1975, a total of 13 888 complete twin pairs answered the questionnaire, corresponding to a response rate of 89%. In 1981, the response was only 5% lower. Zygosity determination based on questions concerning the similarity in physical appearance at school age was initially carried out for the entire cohort. The validity of the self-reported zygosity was assessed using genetic markers in a subsample of the cohort, and there was 100% consistency between the results of the questionnaire and the genetic test for those whose zygosity had been classified, while approximately 7% were left unclassified (Sarna et al. 1978).

#### *4.1.2 Variables describing Finnish twins*

The postal questionnaires included a wide range of questions on current and past health, health behaviour and socio-economic conditions. Respondents were asked to classify their education according to one of eight categories, which were then converted to either 3, 6, 7, 9, 10, 12, 13, or 16 educational years and analysed as a continuous variable (Silventoinen et al 2000a).

Midlife BMI was determined as an average of the BMI in 1975 and 1981, or as the value in one of these years if the weight and height were not reported in both years. To analyse the association between different categories of weight and cognition in old age, subjects were classified into three groups according to their BMI, with values lower than 25 kg/m<sup>2</sup> indicating normal weight, from 25 to 30 kg/m<sup>2</sup> overweight and higher than 30 kg/m<sup>2</sup> obesity. Subjects reporting a notable weight loss or gain were compared to those reporting a lesser weight change. In analysis of the association between midlife height and cognition in old age, the height reported in 1975 was preferred, since age-associated shortening was most likely to be less that time. The reliability of self-reports of weight and height was earlier found to be good in this same twin cohort (Korkeila et al. 1998).

Histories of cardiovascular disease, hypertension, hypercholesterolemia and diabetes were established according to the questionnaires, hospital discharge registry records and records of the Social Insurance Institution for reimbursed medication, which have an extensive coverage for chronic conditions. In Finland, medication for these diseases is fully or nearly fully reimbursable. To qualify for reimbursement, a certificate from the treating physician is reviewed by physicians at the Social Insurance Institution and needs to meet specified diagnostic criteria. Access to records was based on permission from the appropriate authorities and carried out by record linkage using the unique personal identification number assigned to all Finnish residents.

Coffee drinking was assessed in both years by asking the number of cups of coffee drunk daily. If reported in both years, their average was calculated. Respondents who did not drink coffee daily were advised to answer zero. Tea consumption was also assessed by a congruent question in both surveys. Tea consumption was minimal compared to coffee consumption, and caffeinated soft drinks were not widely consumed in Finland at the time of the surveys. Since cognitive impairment and dementia are more strongly associated with a binge-drinking pattern than with a particular level of alcohol consumption (Järvenpää et al. 2005), we considered binge drinking of alcohol as a confounding variable. Those reporting drinking more than one bottle of wine, half a bottle of spirits or the equivalent amount of other alcoholic beverages on the same occasion at least once a month in 1975, 1981 or in both years were considered as binge drinkers.

Life satisfaction and smoking status were based on the 1981 questionnaire or on that in 1975 if not reported in 1981. Life satisfaction was assessed with a 4-item scale and subjects were classified as satisfied, moderately satisfied or dissatisfied (Koivumaa-Honkanen et al. 2004). Categories of never, occasional, former and current smokers were established according to reports of current and past smoking (Kaprio and Koskenvuo 1988). Leisure-time physical activity was based on reports of the frequency, mean duration and intensity of leisure activity in 1975 and 1981, or just one of these if not reported in both years. The metabolic equivalent (MET) index was calculated for each activity by assigning a multiple of resting metabolic rate (MET score) varying from 4 (exercise intensity corresponding to walking) to 13 (running), and the product of the intensity, duration and frequency of activity was calculated (Kujala et al. 1998).

The availability of blood samples from 73% of study population allowed an assessment of the association between BMI and cognitive performance in subgroups based on the subjects' ApoE status. If subjects had earlier provided DNA, written consent was obtained for this study at the same time as the subjects were asked to participate in a telephone interview to determine their cognitive status (see 4.2.1). Other subjects were asked to offer a venous blood sample at the local health centre and return it to the National Public Health Institute, where genotyping was performed (Virta et al. 2010). Subjects were classified according to the number of ApoE  $\epsilon$ 4 alleles, and those having 1 or 2 alleles were compared with those having none.

#### *4.1.3 Danish twins*

Danish subjects belonged to the Longitudinal Study of Aging Danish Twins (LSADT), which is a sample drawn from the older cohorts of the Danish Twin Registry, including all Danish twin pairs born between 1870 and 1910 and all same-sex twin pairs born between 1911 and 1930 (Hauge 1981, Holm 1983). Sampling of the original twin registry was carried out from the regional population registers and other public sources in 1954, and the first questionnaires were sent to the participants as soon as they were traced. The zygosity of same-sex twins was assessed in the first postal questionnaire, and a later comparison of zygosity determination based on questionnaire items and blood group determinants found a misclassification rate of



less than 5% (Hauge 1981). Due to a problematic zygosity determination of twins whose partners died or emigrated before the age of 6, they were not followed up.

This study is restricted to the first wave of the LSADT containing all 3099 registered Danish twins who had not permanently emigrated, were 75 years or older and alive in January 1995, when they were contacted again by post and asked for permission for an interviewer to visit their residence and conduct a health-related, one-hour, face-to-face interview. Subsequently, the surviving members of the initial cohort have been visited by interviewers who go through essentially the same procedure every second year. Since the LSADT uses a cohort sequential design, additional cohorts have been added in order to disentangle the genetic and environmental contribution to physical and cognitive aging (Skytthe et al. 2006).

#### *4.1.4 Variables describing Danish twins*

Questions on background demographics, self-related health, diseases, medications, activities of daily living, physical and cognitive abilities, depression, and life circumstances and events were included in the study protocol. In addition, objective tests were performed such as hand grip strength assessing physical functioning (Frederiksen et al. 2002), MMSE, and a composite of three individual cognitive measures (fluency task, forward and backward digit span, and immediate and delayed recall) assessing cognitive functioning (Christensen et al. 1999). Within-pair correlations between each of the cognitive tests (including their composition) and MMSE ranged from 0.49 to 0.64, indicating only a moderate correlation between them. Moreover, bivariate Cholesky decomposition revealed a genetic correlation of 0.71 (95% CI = 0.58;0.81) and an environmental correlation of 0.44 (95% CI = 0.32;0.55) between them, also indicating a substantial proportion of non-shared underlying factors (McGue and Christensen 2001). Thus, only the results of MMSE were used in this study to analyse the association between old age cognition and height, which was measured as part of the examination procedure.

The socioeconomic status (SES) based on earlier employment of the participants was taken into account in this study. The leading principle of social classification was an individual's position in relation to production, i.e. control over the working situation irrespective of

whether this was gained through ownership of the means of production, through subordinates or attained through education. For instance, independent businessmen with large concerns, employees with a large number of subordinates and persons with a high level of education belong to one and the same social class.

## *4.2 Cognitive assessment*

### *4.2.1 Finnish twins*

All twin individuals aged 65 or older were asked to participate in a telephone interview in order to define their cognitive status. MZ twin individuals with both co-twins alive were interviewed between the years 1999–2001 and same-sex DZ twins and twins of uncertain zygosity (irrespective of the status of their twin sibling) between the years 2003–2007. Each subject was sent a letter containing information about the study a week before the interview, and their consent was asked at the beginning of the phone call. The interviews were carried out by two research nurses, who were blinded with respect to any subject's cognitive status. The study protocol was approved by the joint Ethical Committee of the University of Turku and Turku University Central Hospital.

Cognitive status was defined by using a combination of two telephone screens (appendix), referred to as TELE (Gatz et al. 1995) and TICS (Telephone Interview for Cognitive Status) (Brandt et al. 1988). Both screens are sensitive and specific instruments for differentiating even mild AD patients from healthy controls and correlate strongly with clinical measurements of cognitive function such as the MMSE (Järvenpää et al. 2002). Questions measured orientation, long-term and short term-memory, attention, abstraction, calculation, language, repetition and non-verbal praxis, and those questions included in both screens were asked once. The total score of this 20-item interview formed a linear variable representing cognitive function which is referred to as the cognitive score.

In order to quantify the risk for mild impairment of cognitive function and dementia in relation to different categories of coffee drinking and BMI, subjects were classified into three categories of cognitive function (possibly demented, cognitively impaired and healthy)

according to their TELE and TICS scores by using earlier validated cut-off scores (Järvenpää et al. 2002). In general, low scores indicate dementia and high scores normal memory.

The telephone interview was completed for 2483 twins of known zygosity (703 MZ twins and 1780 DZ twins) and 123 twins of uncertain zygosity with an overall response rate of 78%. The mean age of the respondents was 73.6 years (SD = 4.7) in men and 75.4 years (SD = 5.7) in women (48% were women). Among those who were not interviewed, 127 were not reached by telephone, 412 declined to participate in the interview, 32 died before being contacted and 133 were not contacted or their interviews were not completed. For the MZ twins, those who participated were more often men, but after adjustment for sex they did not differ from non-participants in age, education or reported alcohol use (Järvenpää et al. 2005). However, among those who had reported their alcohol consumption in midlife, the non-interviewed were older and less educated (Virta et al. 2010). The earliest hospitalization for dementia (ICD9 rubric 290) was in 1993, while 3% of the subjects had been prescribed medications (memantine, donepezil, galantamine or rivastigmine) for dementia after 1996, when they became reimbursable by Social Insurance Institution. However, cognitive status was only based on the results of the telephone interview in this study.

#### *4.2.2 Danish twins*

In 1995, a total of 2401 assessments were performed by trained interviewers from the Danish National Institute of Social Research, corresponding to a response rate of 77%. A total of 1% of the potential study population took part in only a partial interview due to the inability to complete it, 9% did not wish to participate in the full interview (provided only general health information) and 13% declined all assessments. The participants and non-participants were similar in terms of age distribution, the MZ:DZ ratio and earlier morbidity based on hospitalization data (Christensen et al. 1999), but participants were significantly more likely to be men (McGue and Christensen 2001).

MMSE was available from 2161 respondents, whose mean age at the time of cognitive assessment was 81.6 years (SD = 4.6) in men and 82.1 years (SD = 4.8) in women (63% were women). Participants with severe physical or cognitive impairment were interviewed by

proxy, which was the major reason for not completing the cognitive assessment and thus not being included in the present study.

### *4.3 Data analysis*

In general, two kinds of analysis were used. Basic models refer to those in which subjects were treated as individuals by using the cluster option in Stata, which takes account of the dependence of individual observations of the twin sample (clustering within pairs) to obtain the correct confidence intervals (Williams 2000). Genetic models utilize the means of quantitative genetics and include estimation of heritabilities, genetic and environmental correlations and the construction of GxE models, which require the use of a twin sample. They also include some basic analyses based on comparisons of MZ and DZ twins or twin siblings discordant for trait in question.

#### *4.3.1 Basic models*

Linear regression analyses were used to estimate the associations of midlife coffee drinking (II), BMI, other midlife metabolic variables (III), height (IV) and cognitive performance in old age. Confounding variables, which were included as covariates in the models, included education/SES, age, sex, binge drinking of alcohol, smoking, life satisfaction, physical activity, ApoE  $\epsilon$ 4 allele and several metabolic conditions (see 4.1.2 and 4.1.4).

The odds ratios (OR) for possible dementia and mild impairment of cognitive function in relation to midlife coffee drinking and BMI were estimated by using multinomial logistic regression analyses. Basic modelling was carried out by using Stata statistical software versions 9.2 and 11 for Windows.

### 4.3.2 Genetic models

Paired two-directional t-tests were used to test the differences between the means of cognitive scores within twin pairs discordant for categorized baseline variables by using Stata. Since a comparison of genetically identical (MZ) or half similar (DZ) individuals excludes/minimizes the genetic contribution to interindividual differences, a significant association within a discordant twin pair suggests a direct causal relationship between the variables under study.

Within-pair intraclass correlations of MZ and DZ twins were computed by Stata and they were compared to each other in order to select an appropriate univariate model (ACE or ADE) for the starting point of genetic analyses. The fits of the initial models were compared with the saturated model, which does not assume the same means and variances of the first and second twin in the pair as well as MZ and DZ twins (i.e. assumption of twin models). The most parsimonious models were searched by comparing the fit of models containing fewer variables to the models from which they were nested, and the standardized effects of variance components were estimated under the best-fitting models (I, IV). These genetic models were carried out by using the Mx statistical software version 1.7.03 and the raw data option, which also allows the inclusion of twins without information on their co-twin in the analyses (Neale 2003).

In Studies I and III, genetic and environmental correlations were computed by using bivariate Cholesky decomposition in which the covariation between two traits (i.e. coffee consumption in 1975 and 1981 in study I and midlife BMI and old age cognitive score in study III) were decomposed into genetic and environmental components by using the relative similarity of MZ and DZ pairs as the basis for genetic modelling.

In Studies I and IV, changes in the additive genetic and unique environmental variance in coffee consumption (I) and cognitive performance (IV) with respect to age (I) and height (IV) in linear (I,IV) and quadratic (I) GxE models were tested.

## 5. Results

### 5.1 Coffee consumption and its genetic architecture (paper I)

Men drank an average of 5.2 (95% CI = 5.1;5.4) and women 5.3 (95% CI = 5.2;5.5) daily cups of coffee. Female sex, a lower educational level, higher BMI and former and current smoking were significantly associated with an increase in coffee consumption, whereas occasional smoking, binge drinking of alcohol, life satisfaction and metabolic conditions were not.

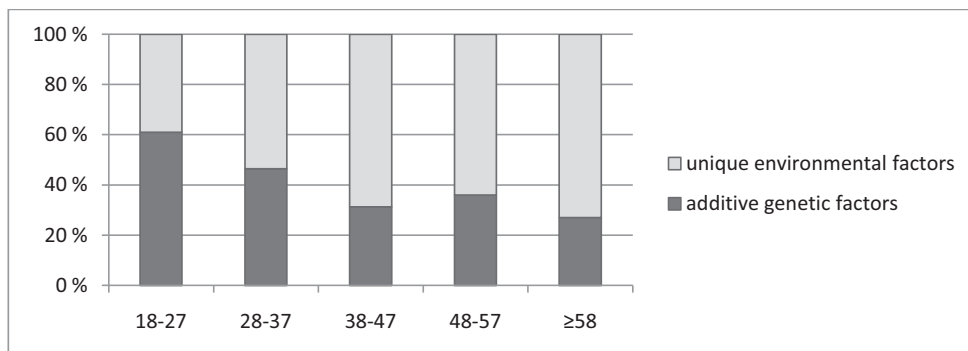
Genetic twin models were performed in a sample of 10 716 complete twin pairs who had reported their coffee consumption in 1975 or in both years (complete of 8124 twin pairs). In genetic modelling, a search for an appropriate initial model and all further analysis were carried out separately for each year, age group and sex. In most subgroups, a comparison of MZ and DZ twins suggested the ADE model (i.e. the correlation within DZ twins was less than half that within MZ twins), which was selected and compared to the saturated model. Comparison of the ADE model with the saturated model revealed a less than optimal fit in two age groups among men in both years and in three and four age groups among women in 1975 and 1981. Thus, the fit was not optimal in most age groups of women. Differences in the means and variances of coffee drinking between MZ and DZ twins are a likely explanation, and thus require further attention. Notably, consistent differences between means or variances may indicate an unequal childhood environment between MZ and DZ twin pairs. In this case, consistent differences between MZ and DZ means would be expected. However, the differences were not consistent in their relationship to zygosity and thus did not indicate a need for a more complex model such as a sibling interaction model. Instead, they were most probably due to random variation, which becomes statistically significant in a large sample leading to a significant difference between the ADE and saturated model.

In a comparison of the ADE model with a simpler AE model, significant evidence of the D effect was only found among the oldest women in 1981. A final comparison of the AE with the ACE model in those 9 subgroups where omitting the D effect had no influence on the model fit ( $p = 1$ ) did not indicate any evidence of a C effect (see 2.3.3). Thus, coffee

consumption was best explained by a combination of additive genetic and unique environmental factors.

The heritability of coffee drinking was 51% in men and 52% in women (an average of 1975 and 1981), and differed substantially between sex and age groups ( $P < 0.0001$ ). Variance in coffee consumption was most heritable in younger subjects, and heritability decreased towards middle age. In older age groups ( $\geq 58$  years), heritability estimates were comparable to those seen in middle age (38–47 years) for both men and women, but slightly increased in men and decreased in women during the time between.

3a.



3b.

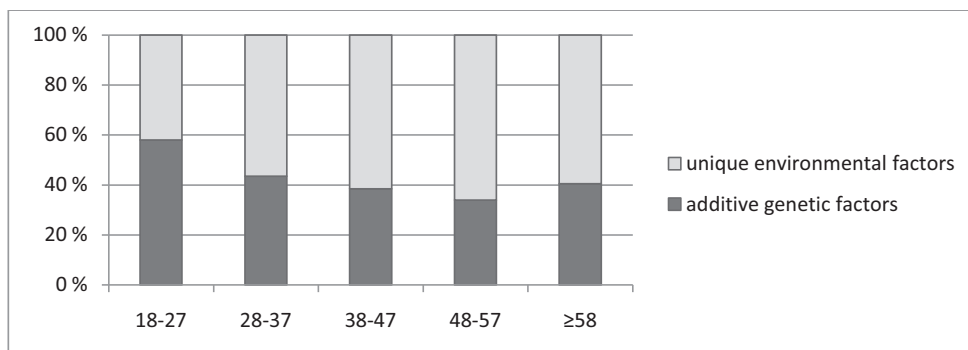


Figure 3. Univariate model results showing the proportions of genetic and environmental factors affecting the variance in coffee consumption under the best-fitting (AE) model in different age groups among men (3a) and women (3b) (an average of two study years).

The results of GxE analysis reinforced the modifying effect of age on genetic and environmental variances in addition to the means of coffee drinking. Both linear and quadratic (Figure 4) modification effects were statistically significant, except for the quadratic effect in women in 1981.

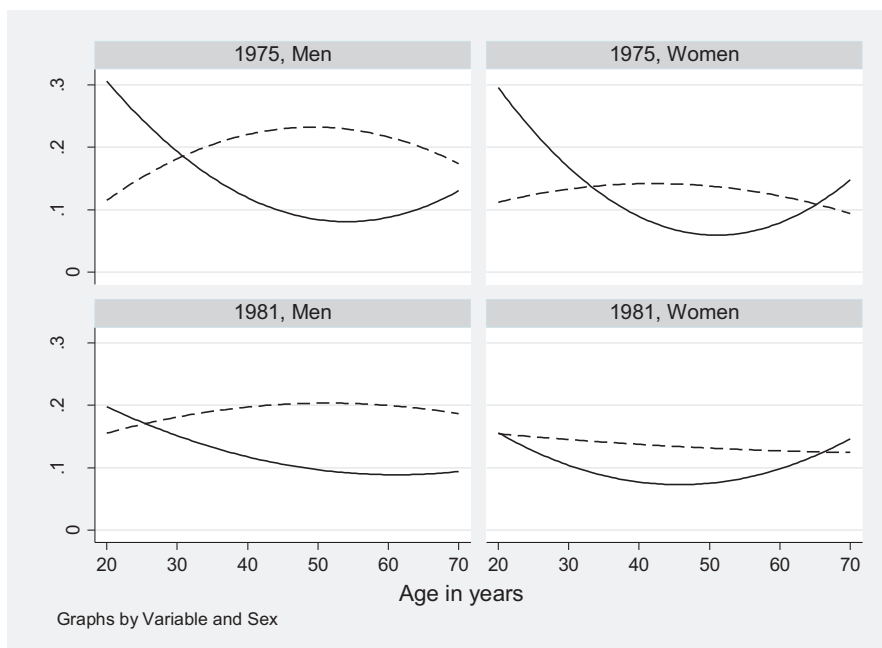


Figure 4. Changes in additive genetic (continuous line) and unique environmental (dashed line) variance as a function of increasing age in the quadratic GxE model.

The six-year correlations of coffee drinking varied between 0.57 and 0.69 (Figure 5). Coffee drinking was most stable in middle-aged subjects and least stable in the youngest subjects. In general, coffee consumption was more stable in men than in women, but the changes in relation to age were similar in both sexes, except for the subtle increase in the oldest age group in men compared to the decrease in women.



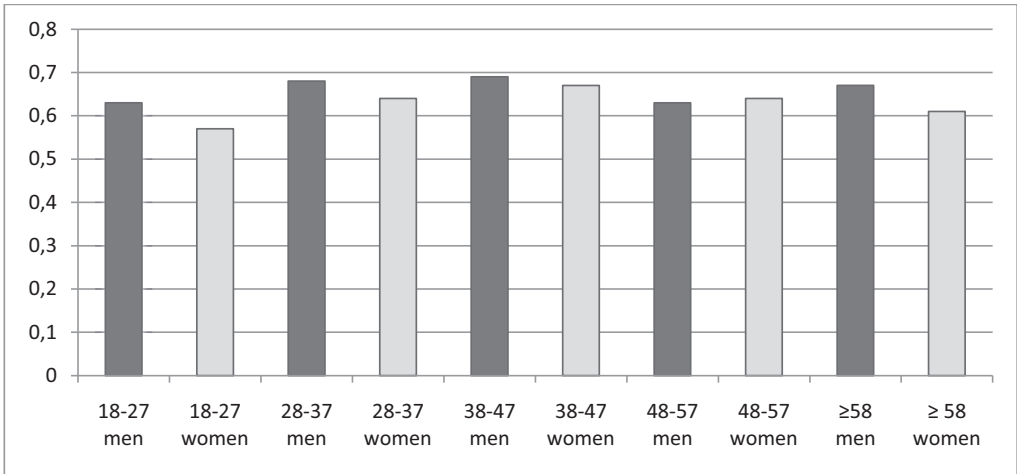


Figure 5. Six-year maximum likelihood correlations of coffee consumption in different age groups of men and women between 1975 and 1981.

The correlation was mainly due to genetic factors in the two youngest age groups, and after that mainly to environmental factors. However, the stability of coffee drinking in old age among women was mainly due to genetic factors, whereas in men environmental factors had a greater role in older age than earlier (Figure 6).

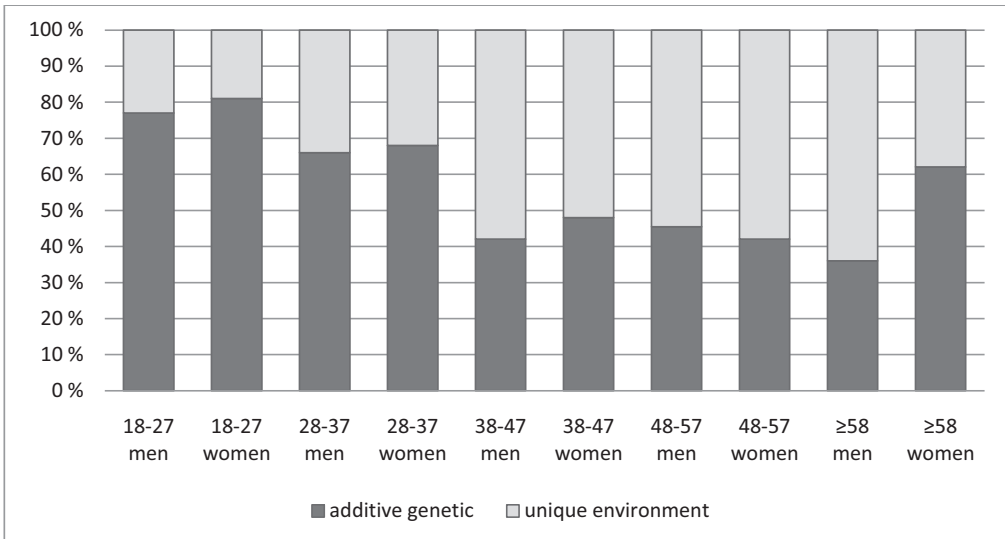
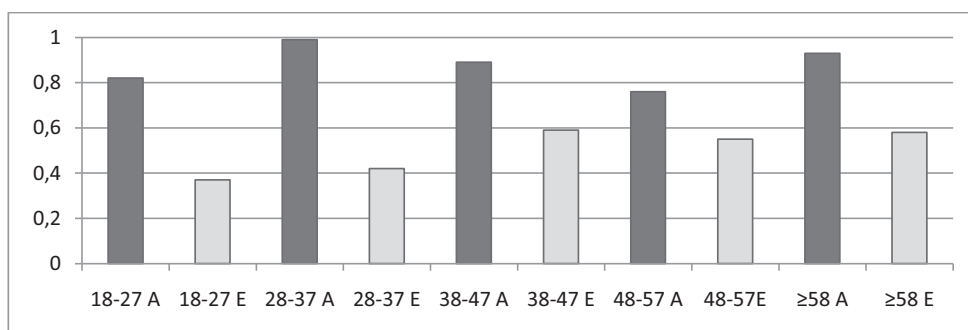


Figure 6. The contributions of additive genetic and unique environmental correlations to the stability of coffee drinking in different age groups of men and women between the years 1975 and 1981.

Genetic factors were stable in all age groups (correlation  $\geq 0.76$ ), and there were virtually no changes in genetic factors among 28- to 37-year-old subjects (correlation of 0.99 in both sexes). Although their stability decreased slightly from then on, the increase was again clearest in the oldest age group (0.93 in men, 1.00 in women) (Figure 7).

7a.



7b.

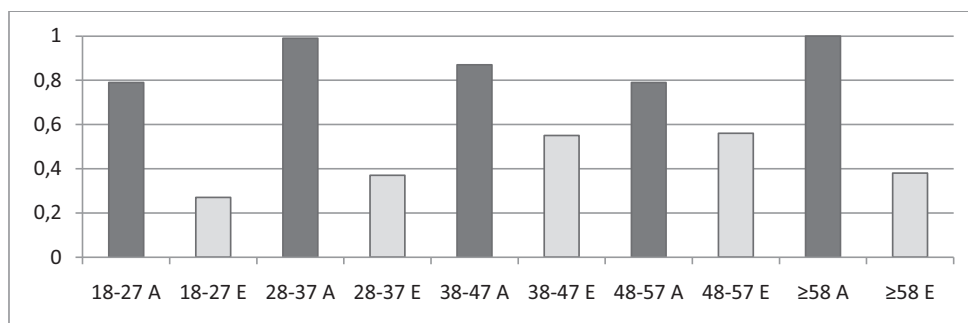


Figure 7. Correlations of additive genetic (A) and unique environmental (E) components affecting coffee drinking in different age groups of men (7a) and women (7b).

## 5.2 Determinants of cognitive impairment in later life and their genetics

### 5.2.1 Childhood environmental factors (paper IV)

The effect of childhood environmental factors on cognitive performance in old age was evidenced by differences in cognitive test scores in relation to height between the Finnish and Danish study samples. Linear regression analyses were performed for standardized cognitive measurements in order to ease the comparison of study cohorts. A greater height was significantly associated with a better cognitive test performance among both Finnish and Danish subjects when adjusted only for age, but significantly so only among Finnish if adjusted for age and education (Table 1).

Table 1. Results of linear regression analyses, i.e. the association between standardized cognitive measurements (in SD) and height (per 10 cm) when adjusted for age or age and education/SES.

|  | Finnish $\beta$ -estimates (95% CI) |                      | Danish $\beta$ -estimates (95% CI) |                                |
|--|-------------------------------------|----------------------|------------------------------------|--------------------------------|
|  | Men                                 | Women                | Men                                | Women                          |
| Adjusted for age                         | 0.28<br>(0.20;0.36)                 | 0.24<br>(0.13;0.34)  | 0.015<br>(0.0023;0.028)            | 0.010<br>(0.0024;0.018)        |
| Adjusted for age<br>and<br>education/SES | 0.18<br>(0.10;0.26)                 | 0.13<br>(0.034;0.23) | 0.0093<br>(-0.0037;0.022)          | 0.0075<br>(-0.00036;<br>0.015) |

In Finnish compared to Danish subjects, the mean cognitive score increased more and there was a consistent decrease in variances (standard deviation, SD) within quintiles of greater height, which was further analysed by performing a GxE model among Finnish subjects. The intraclass correlation of cognitive scores within MZ twins was less than two times higher than in DZ twins, suggesting C in addition to A and E effects (ACE model) on the cognitive score for men and women. Comparison of the AE model with the ACE model showed that C and its moderator effects were not significant in either sex. Thus, further analyses were carried

out by using the AE model including moderators (i.e. to determine how height affected the magnitude of these components) in both men and women.

Omitting the moderator of E had a statistically significant effect in both men ( $\Delta\chi^2_1 = 14.74$ ,  $p = 0.0001$ ) and women ( $\Delta\chi^2_1 = 20.59$ ,  $p < 0.0001$ ), which means that the amount of environmental variance in cognitive performance in old age differed according to height such that the environmental variance was greater among shorter subjects. However, omitting the moderator of the A component has no statistically significant effect in either sex, indicating that genetic variance itself did not change according to height. However, since there was more environmental variation in cognitive performance in shorter subjects, the proportion of cognitive performance explained by genetic factors was consequently higher among taller subjects (Figure 8).

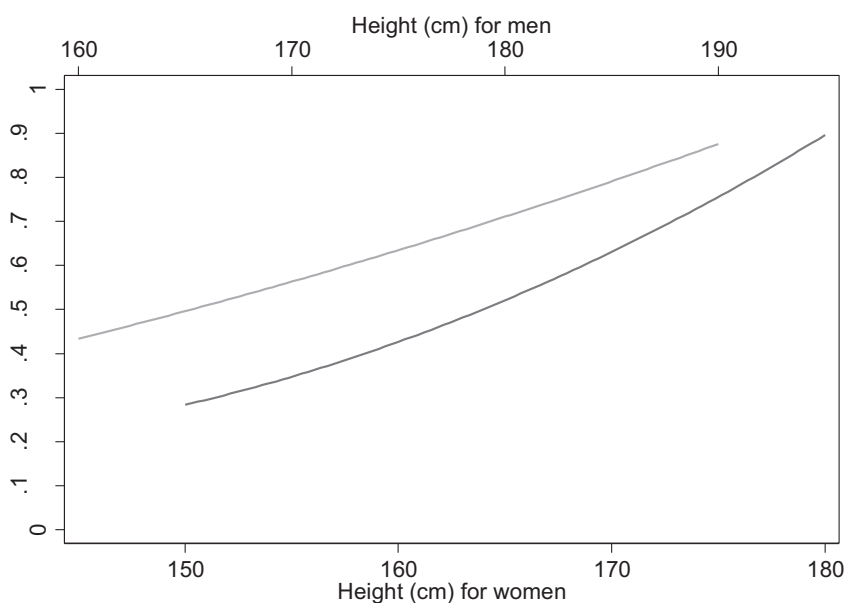


Figure 8. Proportion of variance in cognitive performance attributed to additive genetic effects as a function of the height of subjects (upper line is for men, lower line for women) based on model fitting of the moderator variable in Finnish men and women. The gene-height interaction model implies that environmental factors played a greater role among shorter subjects, whereas the effect of genetic factors was greater among taller subjects.

### 5.2.2 Midlife factors (papers II and III)

The main midlife characters whose effects on cognitive performance in old age were analysed in this study were coffee drinking (II), BMI, weight change and cardiovascular disease, hypertension, diabetes and hypercholesterolemia, which are termed metabolic conditions in this study (III) (Table 2). Taking into account the crucial effects of age and education on cognitive performance, analyses were adjusted for these variables in addition to sex, which was not, however, significantly associated with cognition in old age. The effects of the main variables under study were also tested when other baseline characters were taken into account as confounders. Among these, lower life satisfaction significantly reduced the cognitive score ( $\beta$ -estimate = -0.17,  $p < 0.001$ ), whereas binge drinking of alcohol, smoking and physical activity did not have a significant effect. A weight gain of more than 1.7 kg/m<sup>2</sup> ( $\beta$ -estimate = -0.72,  $p = 0.046$ ) and loss of more than 2 kg/m<sup>2</sup> were significantly associated with a decrease in the cognitive score when adjusted for sex, age, education and BMI. To ensure the lack of any associations in respect to coffee drinking, linear regression was performed separately for the older and younger halves of study population, but neither showed a significant association.

The effect of the ApoE  $\epsilon$ 4 allele on cognitive performance was analysed in a subsample that contained 73% of the study population for which DNA was available. Number of the  $\epsilon$ 4 alleles (scored as 0,1 or 2) was not significantly associated with cognitive performance when adjusted for age, sex and education ( $\beta$ -estimate = -0.32, 95% CI = -0.86;0.22,  $p$ -value = 0.25,  $n = 551$  for one ApoE  $\epsilon$ 4 allele and  $\beta$ -estimate = -1.91, 95% CI = -4.03;0.22,  $p$ -value = 0.078,  $n = 51$  for two ApoE  $\epsilon$ 4 alleles), and thus no further analyses in relation to the ApoE  $\epsilon$ 4 allele were performed.

Table 2. Linear regression analysis results showing associations between midlife variables of main interest in the study and the cognitive score in old age among 2606 Finnish subjects. Adjusted for age, sex and education.

|  | $\beta$ -estimate | 95% Confidence Interval | p-value |
|--|-------------------|-------------------------|---------|
| Female sex                                 | 0.28              | -0.18; 0.74             | 0.24    |
| Age at the time of interview<br>(per year) | -0.44             | -0.38; -0.49            | <0.001  |
| Education (per year)                       | 0.78              | 0.71; 0.86              | <0.001  |
| Daily coffee consumption<br>(per cup)      | -0.04             | -0.13; 0.05             | 0.40    |
| BMI (per kg/m <sup>2</sup> )               | -0.09             | -0.19; -0.01            | 0.04    |
| Weight change (per kg/m <sup>2</sup> )     | -0.097            | -0.25; 0.052            | 0.20    |
| Diabetes                                   | -1.19             | -1.97; -0.42            | 0.003   |
| Cardiovascular disease                     | -0.71             | -1.24; -0.19            | 0.01    |
| Hypertension                               | -0.81             | -1.48; -0.15            | 0.02    |
| Hypercholesterolemia                       | 0.20              | -0.70; 1.10             | 0.67    |

Multinomial logistic regression analyses adjusted for sex, age and education revealed that being overweight in midlife increased the risk of mild impairment of cognitive function according to both interviews (TELE: OR = 1.35, 95% CI = 1.10;1.66; TICS: OR = 1.25, 95% CI = 1.01;1.54), while being obese increased the risk even more (TELE: OR = 2.02, 95% CI = 1.30;3.16; TICS: OR = 1.56, 95% CI = 1.02;2.37). However, the risk of possible dementia was significantly increased only in obese subjects according to the TELE interview (OR = 2.16, 95% CI = 1.33;3.51). Each unit increase in BMI also increased the risk of possible dementia (OR = 1.05; 95% CI = 1.00;1.10) and mild impairment of cognitive function (OR = 1.07, 95% CI = 1.03;1.11) based on the TELE interview. The categories of coffee consumption, including the category of  $\geq 8$  cups/day, had no predictive value for either category of decreased cognition. To test the potential threshold effect of coffee, the consumption of 1, 2 and 3 cups/day was separately compared with 0 cups/day, but no significant associations were found.

Cardiovascular disease significantly reduced the mean cognitive score within discordant twin pairs. No other metabolic conditions showed significant effects when adjusted for age and sex, or for age, sex and education (Table 3). The effect of coffee within discordant pairs was analysed even without any additional adjustments and separately in discordant MZ and DZ pairs, but no associations were found.

Table 3. The results of two-directional t-tests adjusted for sex, age and education showing associations between metabolic variables and cognitive performance within twin pairs discordant in relation to categorized baseline variables (n = number of discordant pairs).

|                        | $\beta$ -estimate (n) | 95% Confidence Interval | p-value |
|------------------------|-----------------------|-------------------------|---------|
| Cardiovascular disease | 1.099 (216)           | 0.25; 1.95              | 0.012   |
| Diabetes               | 0.78 (86)             | -0.70; 2.26             | 0.30    |
| Hypertension           | 0.15 (139)            | -0.87; 1.16             | 0.77    |
| Hypercholesterolemia   | -1.15 (44)            | -3.37; 1.074            | 0.30    |

The correlation between midlife BMI and the cognitive score was significantly explained only by correlation of additive genetic effects ( $r_A$ ) in bivariate Cholesky decomposition. The ACE model was selected for initial analyses, but comparison of the AE model with the ACE model indicated no significant common environmental correlation ( $\Delta\chi^2_6 = 1.07$ ,  $p = 0.98$ ) and a comparison of the AE model with the saturated model suggested that the assumptions of twin modelling were not violated ( $\Delta\chi^2_{35} = 49.3$ ,  $p = 0.07$ ). Since genetic and environmental correlations did not show any significant difference between sexes ( $\Delta\chi^2_2 = 0.99$ ,  $p = 0.66$ ), they were fixed in the model allowing different variance components for men and women. In the AE model, the unique environmental correlation was also non-significant ( $\Delta\chi^2_1 = 0.39$ ,  $p = 0.53$ ). Thus, the best fitting model allowed only additive genetic correlation ( $r_A = -0.12$ , 95% CI = -0.21;-0.03), but it also lost this significance when adjusted for education ( $r_A = -0.06$ , 95% CI = -0.16, 0.03).

## 6. Discussion

### 6.1 Genetic epidemiology of coffee use

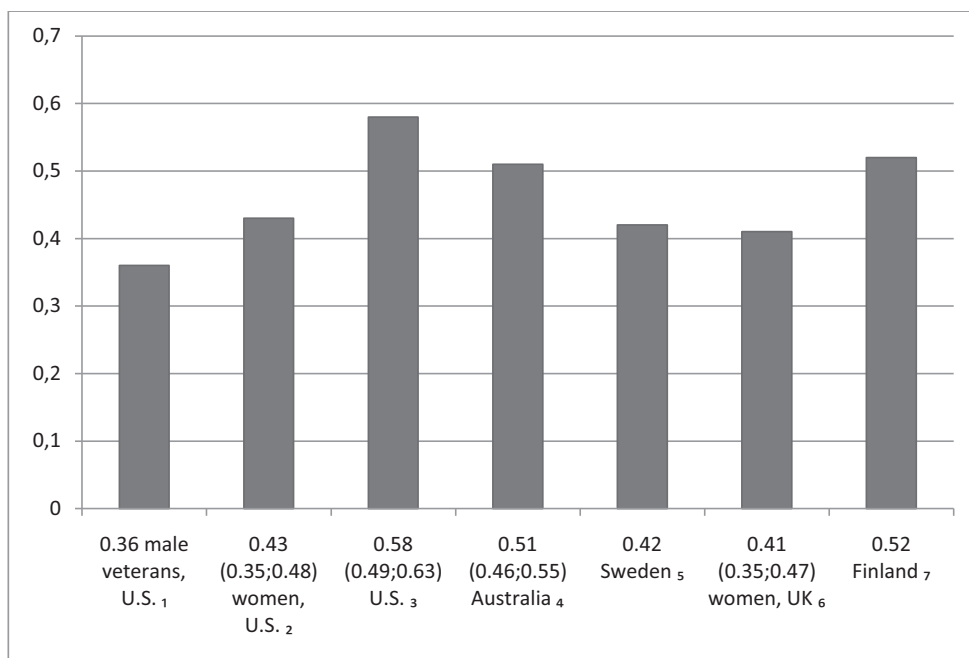
Coffee consumption was high, reflecting the highest global coffee consumption in the Finnish population. The average number of cups of coffee drunk daily was more than considered as heavy drinking in some other studies (Kendler and Prescott 1999, Djordjevic et al. 2008), but was consistent with the findings of another coeval Finnish study, which found that 16% of subjects drank 0–2 cups of coffee per day, 39% more than 5 cups per day, and the majority of study population a number of cups between these (Eskelinen et al. 2009). The significant associations with coffee consumption in that study were largely the same as in ours: women, smokers and lesser educated subjects drinking more. The researchers also found that the above-mentioned categories of coffee consumption differed with respect to age at the time of coffee assessment, total cholesterol in midlife and depression in old age (age was associated with a lower coffee consumption, whereas serum cholesterol and depression associated with higher consumption). In our study, age, the right to drug reimbursement due to hypercholesterolemia and lower life satisfaction in midlife were not significantly associated with coffee drinking, whereas higher BMI in midlife associated with a higher coffee consumption.

As coffee is a licit and socially accepted beverage, the reliability of reporting coffee drinking is supposedly high. Moreover, since no notable health effects of coffee were accepted at the time of assessment of coffee consumption, substantial under- or over-reporting of coffee consumption was unlikely. In addition, coffee was widely available and virtually all the respondents were likely to be exposed to coffee drinking. According to a global comparison, differences in coffee consumption according to incomes and income changes were already small at the time of questionnaires, since the elasticity of coffee demand in Finland was among smallest in the world (Voipio 1993). Coffee was also the main source of caffeine in our study population, since only 53% of men and 38% of women in 1975 and 60% of men and 53% of women in 1981 reported daily tea consumption. Among tea drinkers, the mean consumption in both years was two cups per day in both sexes. This coincides with the finding that increased coffee consumption is associated with a decrease in tea consumption



and vice versa (Woodward and Tunstall-Pedoe 1999, Luciano et al. 2005). In addition, caffeinated soft drinks, such as cola beverages, were not widely available at the time when coffee drinking was assessed. Based on these characteristics of the subjects and society, Finns in the 1970s and the early 1980s were an ideal population for coffee research.

The heritability estimates determined in this study (Laitala et al. 2008) were largely similar to those of previous studies, which have ranged from 0.36 to 0.58 (Swan et al. 1996, Hettema et al. 1999, Kendler and Prescott 1999, Luciano et al. 2005, Reynolds et al. 2006, Teucher et al. 2007) (see Figure 9).



<sub>1</sub> Swan et al. 1996, <sub>2</sub> Kendler & Prescott 1999, <sub>3</sub> Hettema et al. 1999, <sub>4</sub> Luciano et al. 2005, <sub>5</sub> Reynolds et al. 2006 (0.00;0.64 in men, 0.47;0.80 in women), <sub>6</sub> Teucher et al. 2007, <sub>7</sub> Laitala et al. 2008 (0.52;0.58 in men and 0.59;0.62 in women in 1975, 0.42;0.49 in men and 0.44;0.46 in women in 1981)

Figure 9. Heritability estimates and 95% confidence intervals (if reported) in parentheses found in existing studies (publications in chronological order). The remaining proportion of variance was explained by unique environmental variance.

Similarly to this study, none of these earlier studies reported significant evidence of a C effect, and all except one (Kendler and Prescott 1999), which suggested the ADE model, ended up with the AE model for coffee or caffeine use. Since none of these other studies investigated the effect of age on heritability, it remains unclear whether and to what extent the heritability estimates differed with respect to age within other study populations. Since the heritability estimates of various age groups in this study differed by up to 0.34 in men and 0.24 in women, differences within other populations can also be expected, and the differences in study results may be due to age differences between study samples. Moreover, in addition to age, the effects of social, economic and ideological factors (i.e. the cohort effect) can be demonstrated in different age groups.

The potential genes affecting coffee consumption include those responsible for coffee and caffeine addiction (Yeomans et al. 2002, Rogers et al. 2003, James and Gregg 2004). Indeed, caffeine tolerance ( $h^2 = 0.40$ ) and withdrawal ( $h^2 = 0.35$ ) were found to be nearly as heritable as the use of caffeine ( $h^2 = 0.43$ ), whereas heavy coffee drinking (at least 5 daily cups corresponding to 6% of the study population) was even more heritable ( $h^2 = 0.77$ ). In addition, the “toxic” effects of coffee drinking, such as feeling shaky or jittery, showed substantial heritability ( $h^2 = 0.45$ ) (Kendler and Prescott 1999). The evidence of a common genetic pathway affecting the joint use of coffee, alcohol and tobacco supports the role of genes related to general addiction. This common pathway has been shown to represent 28% in women (Hettema et al. 1999) and 33% (Hettema et al. 1999) and 28% (Swan et al. 1996) in men of the total genetic component of coffee drinking. Furthermore, genes associated with taste perception are of potential interest. For instance, people who were able to taste 6-n-propylthiouracil rated caffeine more bitter and liked it less (Ly and Drewnowski 2001).

In addition, interindividual differences in the metabolic pathways of caffeine elimination may increase the variation in coffee drinking. Indeed, significant interindividual differences have been reported in the urinary ratio of caffeine metabolites, reflecting systemic caffeine clearance (Campbell et al. 1987). In particular, differences in the activity of the CYP1A2 enzyme, representing around 15% of the total cytochrome P450 content of the liver and responsible for 90% of the primary caffeine metabolism in humans (Tassaneeyakul et al. 1994), may be responsible for this variation. Interestingly, there are more than 40-fold variations in the CYP1A2 messenger RNA content in the human liver (Schweikl et al. 1993). Caffeine metabolism, i.e. CYP1A2 activity, was found to be mainly under genetic control ( $h^2$

= 0.73) (Rasmussen et al. 2002), induced by the consumption of at least 3 daily coffee cups (Djordjevic et al. 2008) and smoking, and inhibited by oral contraceptives (Rasmussen et al. 2002, Ghotbi et al. 2007). The inducing effect of smoking could also partly explain the joint use of coffee and tobacco.

Environmental factors affecting coffee consumption were found to be unique for each twin individual, consequently representing environmental exposures and experiences not shared with their co-twins, and thus typical of adult age. Studies on a wide range of dietary habits have found no or only a minor effect of common environmental factors on dietary habits among adults (van den Bree et al. 1999, Teucher et al. 2007, Keskitalo et al. 2008), although they are strong during childhood (Breen et al. 2006). Environmental factors in this study were likely to derive from the work environment, since they were most stable and had the strongest influence among middle-aged and older subjects, who were most likely to have had a steady work place and community. Indeed, a “statutory coffee break” is a fixed convention in Finnish working culture in the whole range of working places.

The lowest stability of environmental factors among the youngest subjects indicates that they were most likely to experience changes affecting coffee drinking in their lives (including social relationships and work), or that their coffee drinking habits were most prone to environmental changes. Since brain maturation continues well into the twenties (Tamnes et al. 2010), it is reasonable that the higher stability of genetic factors was found in 28- to 37-year-olds than in the youngest subjects. In general, 28- to 37-year-old subjects (and the oldest women) had the greatest stability of genetic factors, while their stability of environmental factors was among the lowest. Conversely, the lowest genetic stability was observed in 48- to 57-year-old subjects, who also had the most stable environmental factors.

A significant modification effect of age on genetic and environmental variation in coffee drinking means that genetic and environmental contributions to coffee drinking differ as a function of age. Since environmental instability would reasonably reduce the stability of genetic factors if interacting with them, it can be speculated that since the highest correlation of genetic factors affecting the six-year correlation in coffee drinking was observed in the age groups showing the lowest correlation of environmental factors, and vice versa, there are unlikely to be uncontrolled GxEs, at least in high amounts. However, on the basis of this observation, the existence of uncontrolled GxEs cannot be excluded, and certain thresholds

for environmental factors (i.e. only stable environmental factors would be strong enough to change gene expression) may exist. For instance, the effects of inducers or suppressors of CYP1A2 could represent other potential GxEs.

Spouse correlations, explained only by phenotypic assortment and not by social homogamy, ranging from 0.20 to 0.24 have been demonstrated for caffeine and coffee consumption (Price and Vandenberg 1980, Reynolds et al. 2006). However, spouse correlations with respect to alcohol (0.41) and tobacco consumption (0.26) were found to be much stronger (Reynolds et al. 2006). Nevertheless, spouses may affect each other and become more similar during the years of living together. Indeed, a spouse correlation of 0.44 was found in a study on older couples (Graham and Braun 1999). This convergence among spouses also increases spouse similarity and may lead to overestimation of initial assortment effects. Moreover, no significant evidence of a common environmental effect, which is a statistical consequence of assortative mating (see 2.3.4), was found in this or most previous studies. In addition, since the initial estimate of the spouse correlation of coffee consumption was already relatively low, nonrandom mating with respect to coffee drinking is unlikely to occur.

In the case of spouse convergence, a greater similarity of MZ female twins compared to male twins in most age groups, and especially in the older ages, may indicate that wives influence their husband's coffee drinking more than vice versa. Indeed, the environmental contribution to the stability of coffee drinking in the oldest men was higher than in younger men, although it was mainly due to genetic factors in the oldest women. On the other hand, the greater similarity of MZ female twins may also be due to greater social interaction among MZ female twins compared to male MZ twins, as has been well documented in earlier studies on alcohol use (Kaprio et al. 1992).

More than one latent liability can affect the use of some substances. In cases where the initiation and amount of consumption have different determinants, the number of abstainers is usually clearly higher than those consuming the least. In addition to those who have never tried, the group of abstainers may include those abstaining on the grounds of their ideology, health condition or other sensitivities, which may partly have a genetic background. For instance, the polymorphism of aldehyde dehydrogenase 2 (ALDH2), an enzyme involved in alcohol metabolism, plays a notable role in interindividual differences in alcohol drinking, and individuals homozygous for a certain allele (ALDH2\*2/\*2) experience strong unpleasant

physiological and psychological reactions after ingesting even a small amount of alcohol, which prevents them from virtually any alcohol consumption (Chen et al. 2009).

However, the existence of only one liability affecting coffee consumption is reasonable, and subjects reporting no daily consumption were thus included in the analyses of this study. In 1975, they represented only 6.3% of men and 5.3% of women, and the respective figures in 1981 were even lower (4.7% and 3.5%). Since the frequency of less than daily coffee consumption was not questioned, they cannot be considered as full abstainers. Although the number of those drinking one cup of coffee per day was less than those who reported no daily coffee consumption, the magnitude of this difference was only small and the proportion of those drinking two cups per day was greater than either of these (Table 4). Also, according to a recent Finnish national survey of the adult population, the proportion of those reporting no daily coffee consumption was less than those reporting 1–2 coffee cups per day (24%), although the number of those reporting no daily coffee drinking had increased substantially since 1975 and 1981 (being 16% in men and 20% in women in 2009). With respect to alcohol consumption, 30.4% reported consuming alcohol at least once a week, whereas 17% consumed alcohol 2–3 times/month, 22% even less frequently and 31% were abstainers (Helakorpi et al. 2010).

Table 4. The number of consumers of 0, 1 and 2 daily coffee cups (data from 1975).

| Number of cups | Proportion of respondents (%) |       | 95% Confidence Interval (%) |          |
|----------------|-------------------------------|-------|-----------------------------|----------|
|                | men                           | women | men                         | women    |
| 0              | 5.1                           | 2.1   | 3.9; 6.4                    | 1.3; 2.9 |
| 1              | 3.0                           | 1.6   | 2.0; 3.9                    | 0.9; 2.3 |
| 2              | 8.3                           | 5.6   | 6.7; 9.8                    | 4.3; 6.9 |

A qq-plot setting the distribution of coffee consumption against a normal distribution found no significant deviation even among those who reported no daily consumption, and heritability estimates for the whole sample compared to those who drank at least one cup/day did not differ substantially.

## *6.2 Determinants of cognitive impairment in later life and their genetic architecture*

The aging population and the lack of disease-modifying treatments for memory disorders highlight the need for research on the prevention of cognitive impairment. Living conditions and environmental prerequisites already present in childhood may have a considerable influence extending years forward, possibly even throughout the course of life. On the other hand, health behaviour and environmental exposures in adulthood also play an important role in health and well-being later in life. Considering both of these expectations, the prevention of common diseases warrants both economic and social investments in a supportive childhood environment, health education and also in services in later life. Similarly to most diseases of old age, interindividual variances in cognitive performance and dementia in old age are also partly due to genetic factors (see 2.1.4.1). Individuals with different genetic or environmental backgrounds may respond differently to risk factors for cognitive impairment.

### *6.2.1 Early life exposures and cognitive impairment in later life*

Childhood environmental limitations, such as malnutrition (Yehuda et al. 2006), chronic diseases (Malleon 1991), behavioural disturbances and psychosocial stress (Skuse et al. 1996), are associated with a slower growth velocity and may restrain the attaining of a height accordant with the genetic potential. Concomitant increases in the heritability of height and national living standards in Finland during the first half of the last century (Silventoinen et al. 2000b) support the contention that a shorter height may reflect the effect of greater environmental restrictions during childhood. This is also supported by results demonstrating that the gap between Finland and Sweden in the average height has narrowed in the cohorts born after the Second World War in tandem with the economic development of Finland (Silventoinen et al. 2001).

In this study, the association between height and cognitive performance in old age among Danish subjects became non-significant when adjusted for SES in addition to age, but not among Finnish subjects when adjusted for age and education. This could be due to

differences in education and SES, which are not fully comparable to each other. Although a high SES can be variously achieved, it is most often associated with a higher educational level (McGarvey et al. 1981, Magnus and Mick 2000, Staff and Mortimer 2008). Moreover, with respect to cognition in old age, the effects of SES, i.e. an individual's position in production and the length of education, can be considered more comparable, since they are both expected to reflect the intellectual duties during the whole of working life. Thus, the clear differences in regression analysis results between the study samples could indicate different mechanisms (or their proportions) underlying a shorter height among Finnish and Danish study groups. Similarly, the greater variance in cognitive scores among shorter Finnish respondents may result from subjects who have not reached their genetically determined height as a result of environmental restrictions and who may have an increased risk for memory disorders in old age.

Early life nutritional deficits are known to increase the risk of common diseases such as cardiovascular disease (Wu and Chen 2009), hypertension (Sawaya et al. 2005), diabetes (Barker 2005), osteoporosis (Nicklas 2003) and possibly degenerative brain diseases such as AD (Borenstein et al. 2006) in later life. In this study, no direct measurement of childhood environment was used. Instead, height in adulthood was considered as an indirect measurement indicating whether the childhood environment had fulfilled the prerequisites of the anticipated growth in height. As a consequence, any environmental factor restricting the growth in height was considered as an environmental restriction, and the effects of those factors with other consequences than a shorter adult stature were not detected at all. Moreover, when using adult height as an outcome of environmental stress, disturbed growth due to environmental restrictions could not be separated from a genetically lower growth potential at the individual level. However, in a large sample of subjects, the group of shortest respondents can be speculated to contain those with most restrictive environment during their growth period.

International comparisons support the differences between the childhood living environment of Danish and Finnish subjects. In the 1920s and 1930s, the Gross Domestic Product in Finland was around half of that in Denmark (Maddison 2003) and in 1950 it was still 35% lower (Figure 10) (Gapminder Foundation 2010a). The difference in childhood conditions is supported by the higher rates of infant (Mitchell 1978, Turpeinen 1979, Amiri et al. 2006) and child mortality (Figure 11) (Gapminder Foundation 2010b) in Finland compared to

Denmark in the first half of the 20th century. For instance, the probability of death before reaching the age of five was 40% higher in Finland compared to Denmark in 1920, varying from 8% to 95% before 1950, when child mortality was still 46% higher in Finland (Gapminder Foundation 2010b). Furthermore, the prevalence of longstanding illnesses in adulthood in Finnish cohorts born before the 1940s was higher than in other Nordic countries, whereas this difference dramatically decreased in cohorts born later, which also suggests the effect of the poorer living environment in Finland until the early 1950s (Silventoinen and Lahelma 2002).

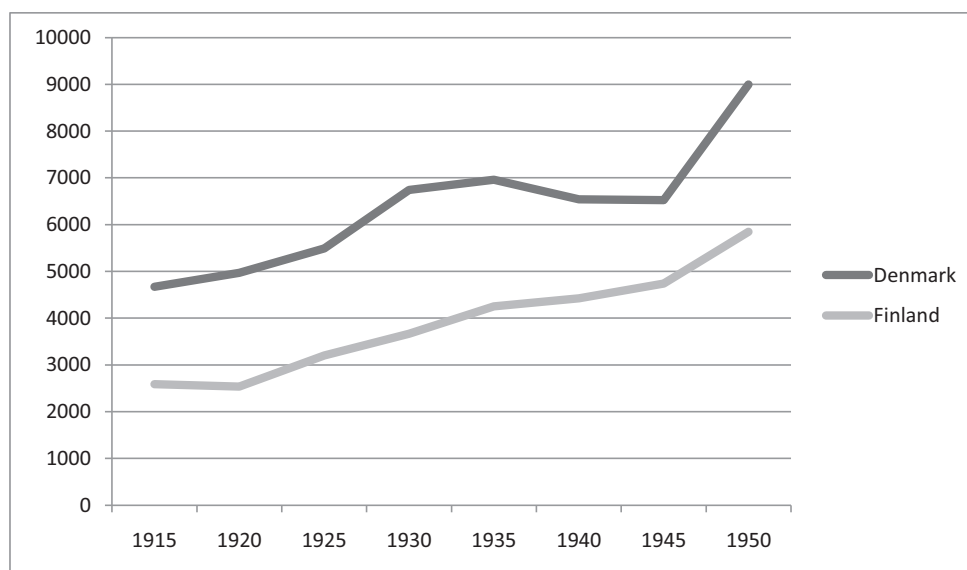


Figure 10. Gross Domestic Product per capita according to Purchasing Power Parities (in international dollars, fixed 2005 prices) in Denmark and Finland between the years 1915 and 1950 (Gapminder Foundation 2010a). Inflation and differences between countries in the cost of living have been taken into account.



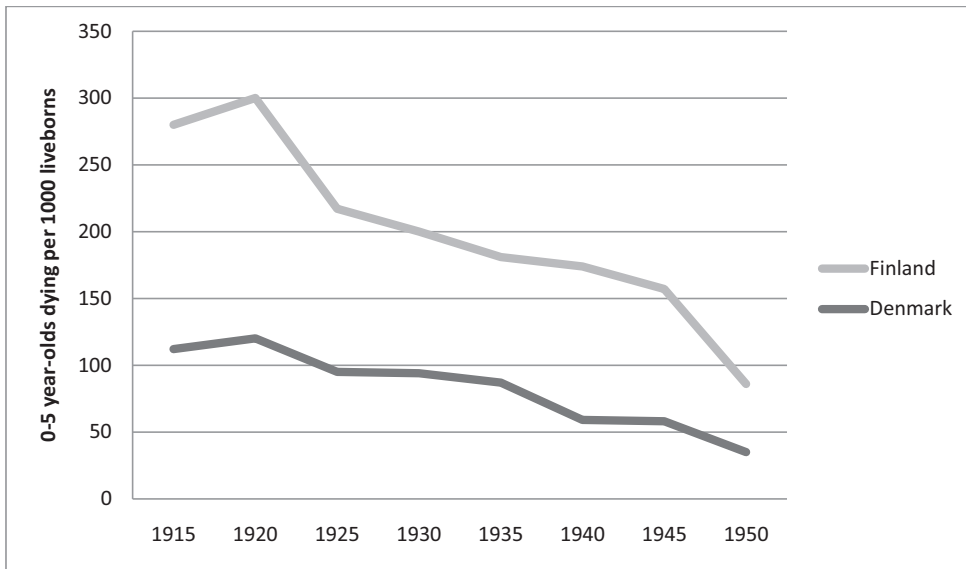


Figure 11. The number of 0- to 5-year-old children dying per 1000 live births in Denmark and Finland between the years 1915 and 1950 according to the Inter-agency Group for Child Mortality Estimation (IGME) (Gapminder Foundation 2010b).

In addition to case-control studies, there have been only two earlier follow-up studies on the association between height and cognition in old age. A follow-up study of 3733 Japanese-American men aged 71–93 years found that a greater height at the mean age of 53 years significantly reduced the prevalence of poor cognitive performance, but not dementia, when adjusted for age and education (Abbott et al. 1998). Another follow-up study of 1892 Jewish men aged 76 to 95 years from Israel with a higher rate of dementia found that midlife height was also inversely associated with AD, VaD and dementia as a whole when including same adjustments and more (Beeri et al. 2005). Height measurement in midlife minimizes the effect of intervening factors, since height-decreasing conditions such as severe osteoarthritis or osteoporosis rarely occur in middle age. In this study, Finnish subjects were also measured an average of 27.5 years earlier than when cognitive performance was assessed, whereas the Danish subjects were measured at the time of cognitive assessment, similarly to most study populations in previous studies.

An association between height and impaired cognition could be explained by the same genetic or environmental factors (or both) affecting each of them. There has been at least one study examining the effect of environmental (i.e. nongenetic) factors that might explain the

discordance for dementia in MZ twins. Although this study demonstrated that a shorter adult height contributed to the risk of dementia at the individual level, no significant differences in height were found among discordant twin pairs (i.e. with one co-twin being demented and other non-demented). Notably, differences in height between MZ co-twins are likely to be only subtle (an average of less than 1 cm in this case) (Gatz et al. 2006b), which may explain the lack of association among discordant twin pairs. Alternatively, different environmental factors leading to a shorter height and dementia could produce similar results.

Little is known about the genetics underlying the association between height and dementia. In one study, a significant height Apoε4 interaction was observed in women but not in men (Petot et al. 2007). In this case, the effect of the Apoε4 allele obscured the association between height and AD. Two other studies found no evidence of a modifying effect of Apoε4 (Moceri et al. 2000, Huang et al. 2008), and although one study recorded opposite effects in odds ratios for dementia in men and women when stratified according to Apoε4, the interaction terms were not significant (Kim et al. 2003). In addition, a large genome-wide association study (GWA) demonstrated that common genetic variants in at least 180 loci influenced adult height, but the APOε4 allele, considered as the most significant SNP associated with AD (Harold D. 2009), was not among them. Furthermore, height-associated variants were found to correlate with variants associated with several diseases, such as diabetes mellitus type 1, T2DM, rheumatoid arthritis, psoriasis and obesity, but not with memory diseases. However, since those 180 SNPs explained only an average of 10.5% of the variance in adult height (Lango-Allen et al. 2010), which is likely to be regulated by many common variants of small effects, there may be some that also correlate with specific memory disorders such as AD (Seshadri et al. 2010).

In twin analyses, rather than identifying single genes, genetic and environmental factors are usually represented as a whole and the modifying effect of a single genetic or environmental factor can be examined more thoroughly by performing interaction models (see 2.3.5). This study examined the effect of height, which was treated as an environmental indicator representing the childhood living environment, on both the genetic and environmental variance of the cognitive score. The results suggest that restrictions during the growth period may lead to greater vulnerability to environmental stressors not shared by both co-twins, leading memory impairment. Since childhood environmental factors affecting cognitive performance in old age are likely to be strong and long-standing, it is unlikely that only one

co-twin would have experienced such exposures in childhood. Thus, these risk factors are most likely encountered during later life. However, in people who have not experienced restrictions leading a lower height, cognitive performance in old age mainly seems to be determined by their genotype. As a consequence, the greater vulnerability to environmental risk factors of the shortest subjects should be considered in classical risk factor studies, and whether the shortest subjects should be excluded needs to be determined on the grounds of the population in question. In genetic research, the lesser impact of genetic factors on cognitive performance in old age among the shortest subjects should be noted.

### *6.2.2 Midlife exposures and cognitive impairment in later life*

Safeguarding of a supportive childhood living environment calls for social institutions and policies, but individual decisions and efforts in later life may at least partly compensate for the exposures of earlier life, which cannot be changed retroactively. Much attention is justifiably given to any supportive evidence of protective factors against cognitive impairment. The central role of coffee in western societies and its previously reported positive health effects may have triggered interest in the potentially positive effect of coffee drinking on cognitive performance. Since epidemiological studies, including this study, show a clear association between vascular disorders and memory impairment (see 2.1.4.2), and they can sometimes also be considered as direct causes of memory disorders (see 2.1.1), it is reasonable that the protective effect of coffee on vascular disorders (see 2.2.3) could also extend to cognitive impairment. Moreover, there are some alternative pathways connecting the effects of caffeine to brain pathology and the risk of cognitive impairment (see 2.1.4.3).

#### *6.2.2.1 Coffee drinking and cognitive impairment in later life*

Some epidemiological studies have suggested a protective effect of coffee on cognitive performance in old age, but their results have been inconsistent (see 2.1.4.3). Although coffee consumption was high and coffee was associated with several baseline characteristics in this study population, midlife coffee consumption did not show any independent association with later cognitive performance in old age. To verify the results, several analyses were

performed. In linear regression analysis, the association between coffee consumption and the cognitive score was only significant when not adjusted for education. This highlights the central role of education in test performance, but does not support the independent effect of coffee. In multinomial regression analysis, coffee drinking did not increase the risk of categories of impaired cognition, and no threshold effect was found. Reasonably, no association was also detected within discordant twin pairs.

The findings of this study must be discussed in relation to previous studies, most of which have concluded that coffee or caffeine could have a protective effect on cognitive performance. Three of five previous studies examining the effect of coffee drinking on cognitive performance found that coffee drinking enhanced the performance in cognitive tests other than MMSE in community- and population-based samples (Jarvis 1993, Johnson-Kozlow et al. 2002, Ritchie et al. 2007, Corley et al. 2010), whereas the two other studies found no association between coffee consumption and a comparable test performance in their study samples of healthy elderly (van Boxtel et al. 2003, Kyle et al. 2010). An association between coffee drinking and better performance in MMSE has been detected in two studies (van Gelder et al. 2007, Santos et al. 2010a), but not in all studies in which MMSE has been performed (Ritchie et al. 2007), and three studies have demonstrated the protective effect of coffee on AD (Maia and de Mendonca 2002, Lindsay et al. 2002, Eskelinen et al. 2009).

The mean follow-up in previous studies has been less than 10 years (Lindsay et al. 2002, van Boxtel et al. 2003, van Gelder et al. 2007, Ritchie et al. 2007, Santos et al. 2010a), except for one with an average of 21 years (Eskelinen et al. 2009). Coffee consumption has also been assessed retrospectively (Maia and de Mendonca 2002, Johnson-Kozlow et al. 2002) or only current consumption has been used (Jarvis 1993, Hamelers et al. 2000, Corley et al. 2010 ). The assessment of coffee drinking in old age is of potential concern, especially in dementia studies, since memory symptoms are expected and subjects at an older age are more prone to several diseases that may lead them to change (probably reduce) coffee drinking. In addition, although we found that coffee consumption was moderately stable over a 6-year period in the Finnish population ( $r = 0.65$  in men and  $r = 0.60$  in women), there may be greater changes in other populations. Thus, coffee consumption in old age may not equate with that in midlife. In this study, coffee consumption was assessed twice and an average of 28 years earlier than cognitive performance, and the association was analysed separately in younger and older

halves of the study population to exclude the effect of a potential decrease in coffee consumption in older ages.

There have been three earlier studies in which the number of subjects has exceeded our sample. One of them found that caffeine protected against a decline in verbal retrieval test results in women but not in two other tests or dementia. However, no protective effect was detected among men (Ritchie et al. 2007). Other larger studies have found that coffee drinking in old age was associated with a reduced risk of AD five years later (Lindsay et al. 2002), and current coffee drinking enhanced the cognitive test performance in subjects under the age of 50 years (Jarvis 1993). Large study samples and strong research frameworks are often needed to publish studies in which associations are not established. Since the largest previous study reporting no association between coffee consumption and cognitive decline included 1376 subjects (van Boxtel et al. 2003), but the smallest study supporting the beneficial influence of coffee drinking contained only 108 subjects (Maia and de Mendonca 2002), there may be several smaller unpublished studies in which no associations have been found. Only recently, a smaller study on 351 older subjects was published in which the association between caffeine intake and slower performance in cognitive tests became nonsignificant after adjustment for SES (Kyle et al. 2010). Similarly, a study on 923 elderly subjects revealed that adjustment for the intelligence quotient at the age of 11 years and SES in adult age, both individually and together, led to a loss of the significant association between caffeine intake and cognitive outcomes in later life. Interestingly, significant positive associations between the intelligence quotient at the age of 11 years and both total coffee and ground coffee consumption were found, indicating that childhood intelligence and other factors including SES, rather than caffeine, may be driving the association with later-life cognition (Corley et al. 2010).

In a recent meta-analysis a significantly lower risk of cognitive decline with respect to coffee drinking was only found when case-control studies were included in addition to cohort studies (risk ratio = 0.84, 95% CI = 0.72;0.99), but not among pure cohort studies which have many advantages when compared to case-control studies. The authors concluded that since the methodological aspects of these studies differed greatly, no robust or definite statements could be provided on the basis of their results (Santos et al. 2010b). Instead of the consumption of certain compounds, such as coffee, the effect of diet as a whole may play a greater role in the prevention of cognitive impairment. For instance, a Mediterranean diet

containing high amounts of antioxidants and unsaturated fatty acids provided a protective effect, whereas the effect of saturated and transunsaturated fatty acids was adverse (Luchsinger et al. 2007).

#### *6.2.2.2 BMI, metabolic conditions and cognitive impairment in later life*

Healthy eating is generally associated with a normal or low BMI, whereas an unhealthy diet is more often associated with overweight or obesity. Nevertheless, the effect of dietary composition on cognition in old age should not be underestimated, since healthy eating habits may also associate with overweight at the individual level (Buckland et al. 2008). This may explain why some studies have found no consistent association between BMI and cognition, although the bulk of epidemiological evidence indicates that a higher BMI in midlife increases the risk of poorer cognition in old age (see 2.1.4.2).

In this study, midlife BMI was generally associated with a poorer cognitive test performance, but also with the categories of impaired cognition. The results suggest that the association between midlife BMI and cognitive performance in old age is partly mediated by metabolic conditions, since adjusting for these led to a loss of statistical significance. In addition, the effect of metabolic conditions on cognition was only significant when not adjusted for BMI, reflecting their strong association. However, it cannot be excluded whether a sample larger than ours (containing more lean subjects with metabolic conditions) would also demonstrate significant associations when adjusted for BMI. This possibility is supported by the fact that dietary habits are also known to associate with metabolic conditions, including T2DM (Martinez-Gonzalez et al. 2008, Nash and Nash 2008, Esposito et al. 2009) and cardiovascular diseases (Nash and Nash 2008), independently of BMI.

An association between a higher midlife BMI and cognitive impairment may reflect either the effect of harmful nutritional factors such as saturated fat, extra adipose tissue gathered in the body, metabolic conditions partly ensuing from a high BMI, or most probably their combination (Figure 12). In addition, several other variables, most notably education, are associated with these, and should therefore be taken into account as confounders in epidemiological studies (Silventoinen et al. 2005, McLaren 2007).

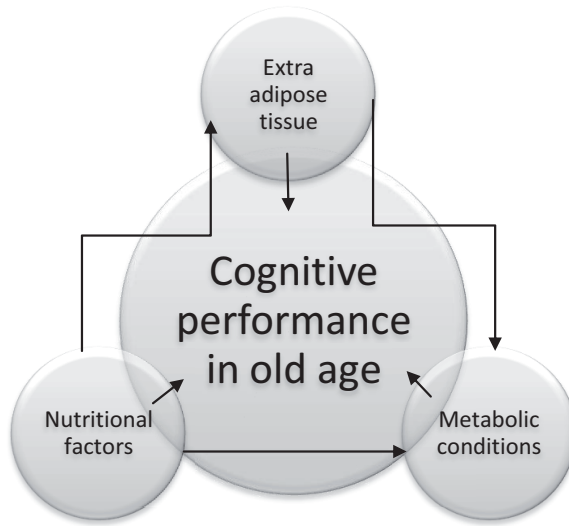


Figure 12. Three diet-related health variables associated with cognitive performance in old age and their causal expectations.

Associations between metabolic conditions and impaired cognitive performance in old age observed at the individual level in this study support the findings of previous studies, and the size of the study population and duration of follow-up were comparable with them. Among the metabolic conditions, diabetes was most strongly associated with cognitive performance. Obviously, we cannot know whether and to what extent this association reflects the effect of hyperinsulinemia, often considered as the main mediating factor, glucose intolerance, and/or adiposity (Luchsinger and Mayeux 2007). Compared to T2DM, previous evidence on the harmful effects of midlife cardiovascular disease (Singh-Manoux et al. 2008), hypertension (Launer et al. 2000, Kivipelto et al. 2001, Qiu et al. 2005) and hypercholesterolemia (Kivipelto et al. 2001) on cognitive performance in old age is less. This highlights the importance of studying them in different populations, including Finns, who have a high national incidence of both potentially harmful metabolic conditions and memory disorders. Significant associations were also found with respect to both cardiovascular disease and hypertension and impaired cognition in old age in this study (Figure 13).

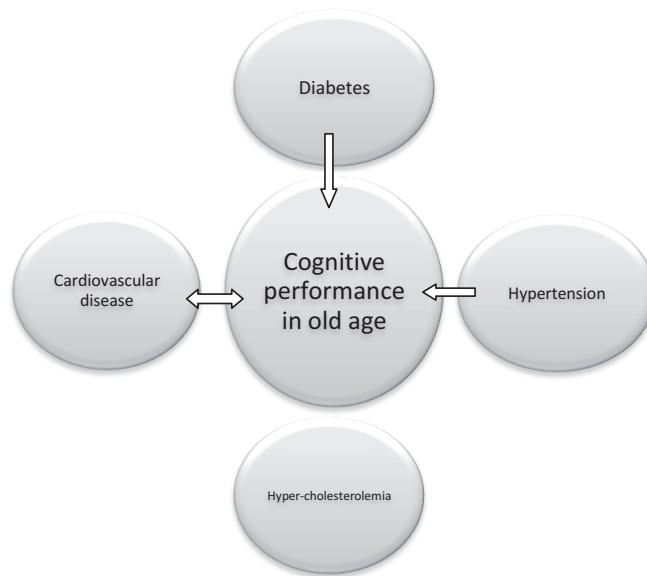


Figure 13. Significant associations between the metabolic conditions under study and cognitive performance in old age at the individual level (unidirectional arrows) and within discordant twin pairs (bidirectional arrow). The latter supports a possible causal pathway between the two variables.

Since dementia-associated weight loss often starts when cognition can be considered only mildly impaired or even earlier (Grundman 2005), studying the effect of midlife weight change requires at least two measurements of BMI several years before the earliest symptoms of memory impairment. Although one study found that a large increase in BMI from early to late midlife was associated with a lower executive function (Sabia et al. 2009), our study demonstrated that a weight change of even half of that within an average of 5.6 years significantly reduced the cognitive performance in old age. The decreasing effect of weight loss on cognitive performance found in our study may be associated with subsequent weight gain and thus reflect the effect of weight fluctuation. Another study investigating the effect of weight change found that weight loss almost doubled the risk of AD compared to a comparable weight gain among women (Beydoun et al. 2008). Thus, the effect of weight fluctuation may be even more harmful than pure weight gain. On the other hand, the possibility that weight loss is a symptom of a process leading to cognitive impairment years later, and not necessarily part of the causal process, cannot be excluded. However, the earliest hospitalization for dementia in this study was only in 1993, and the low proportion of



subjects with prescribed medications for dementia (3%) in 1996 suggest a low incidence of incipient memory disorders at the time when weight loss was assessed.

In this study, the ApoE  $\epsilon$ 4 allele that has been associated with an increased risk of impaired cognition was not significantly associated with cognitive performance when adjustments were made for age, sex and education. However, the results of linear regression analysis indicated a higher risk of poorer cognitive performance when having one ApoE  $\epsilon$ 4 allele, and an even higher risk when having two alleles, and are thus in concordance with those studies in which these associations have been statistically significant. Indeed, the risk increase in relation to having two ApoE  $\epsilon$ 4 alleles was also nearly significant in this study ( $p = 0.078$ ), and significant associations could be demonstrable in a larger sample. Contributions of genetic and environmental factors to the association between BMI and cognitive performance had not previously been studied. We found that the additive genetic correlation was statistically significant, but only if education was not incorporated into the model, indicating that genetic factors associated with education correlate with those of BMI (Figure 14). Indeed, a significant negative correlation between genetic factors ( $r_A$ ) affecting midlife BMI and education was demonstrated in this same study cohort. Among men and women born in 1915–1946,  $r_A$  was -0.18 and -0.21 (Silventoinen et al. 2004), i.e. stronger than the genetic correlation between BMI and cognition in old age found in this study ( $r_A=-0.12$ ).

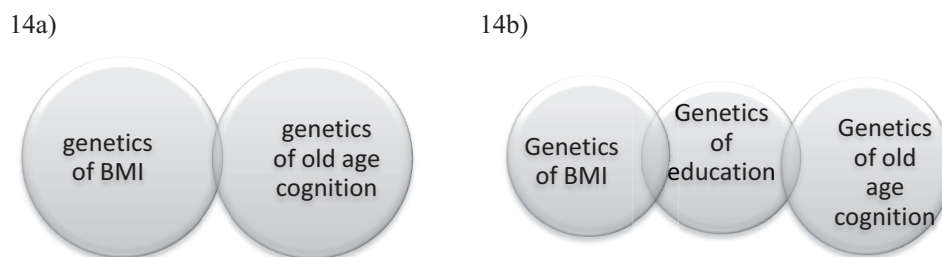


Figure 14. The upper figure (a) represents a situation in which education is not incorporated in the model and there is significant genetic correlation underlying the association between BMI and cognition. The incorporation of education in the model led to a loss of this significance (b).

In fact, the loss of a significant correlation found in this study supports the hypothesis of a causal relationship between BMI and poorer cognition. However, the existence of even a subtle common genetic pathway between BMI and cognition cannot be excluded in the basis of this study, since it could be demonstrable in a larger sample of twins.

### *6.2.2.3 Causal conclusions in epidemiological studies in relation to BMI, metabolic conditions and cognitive impairment in later life*

Conclusions from epidemiological studies should be drawn with particular caution, especially when causal implications are stated. Although biologically plausible associations observed at the population level may suggest causal mechanisms between two variables such as coffee drinking or BMI and cognitive impairment, there may be other plausible mechanisms, such as unnamed common genetic or environmental pathways, connecting two variables, or the associations may be due to coincidence.

In preventive medicine, it is important to differentiate causal relationships from associations indicating an increased risk. For example, dementia-associated weight loss often begins years prior to AD-related clinical symptoms (Knopman et al. 2007). However, a reduction in lean body mass coincides with a reduction in both brain volume and cognitive performance, indicating that dementia-associated weight loss is either a direct or indirect consequence of AD rather than an independent risk factor (Burns et al. 2010). Indeed, midlife obesity rather than weight loss has been considered as a potentially greater risk factor for cognitive impairment (see 2.1.4.2). However, on the basis of association studies, an alternative explanation for a shared genetic or environmental pathway common to AD and sarcopenia, which is also associated with weight loss among the elderly, cannot be excluded (Burns et al. 2010).

In order to make causal inferences, several aspects must be considered. The complete causal mechanism for biological effects, most of which are still unknown, usually involves a number of both genetic and environmental factors correlating and interacting with each other. In practice, this means that even after identifying and excluding one of the component causes, which is not necessary for disease, some disease may still occur. However, identifying the

component causes of common and/or severe diseases is of central importance, since the blocking of any causal component results in the prevention of some disease cases (Rothman and Greenland 2005). The prevention of cognitive impairment, which most often has a multifactorial aetiology, is also reasonable, since many of the potentially risk-increasing factors are also tightly connected to several other common diseases such as ischemic coronary artery disease and ischemic attacks.

Inappropriate causal inferences, i.e. biases, can be minimized through the study design (minimizing the bias due to sample selection, measurements, disease detection, follow-up etc.), but since not all the bias can be removed in epidemiological or other studies, this must be taken into account when analyzing the study data. The traditional approach to confounding is to adjust for covariates in multiple regression models, but since the criteria for confounding variables are not simple, they must be selected with special caution. The causal directed acyclic graph (DAG) is a graphical representation of causal effects between variables (arrows connecting two variables in the map indicate causation), which can be used to help choose covariates in traditional statistical approaches. For example, the repetition of a short step-by-step process can be used to test whether a subset of covariates should be included in the model to minimize the bias (Shrier and Platt 2008). There are also combinations of criteria based on features such as the strength and consistency of the association, developed to distinguish causal from noncausal relations in epidemiological studies (Hill 1965), but a sufficient set cannot be constructed (Rothman and Greenland 2005).

In addition to randomized controlled trials, the causal relations of two variables, i.e. the potential risk or protective factor and the outcome, can be estimated by studying genetic variants if an even distribution of confounding variables is observed with respect to the gene alleles of individuals. Thus, variables lying on the causal pathway between the genotype and the outcome can be distinguished from other variables by combining the results of genotype-risk factor association analysis and genotype-outcome association analysis in “Mendelian randomization” studies. This is based on the assumption that genotypes are only associated with the variables lying on the causal pathway between the genotype and the outcome (Bochud and Rousson 2010). Although there have been no Mendelian randomization studies with respect to ApoE or other genetic alleles and cognitive impairment, the causal relations between cholesterol and cancer have been studied by using the ApoE genotype (Trompet et al. 2009).

In twin studies, the potential effect of a common genetic pathway connecting two variables can be minimized. By comparing the cognitive performance of twins who differed with respect to metabolic characteristics, this study provided further evidence for the likely causal relationship between cardiovascular disease and cognitive impairment demonstrated by a significantly lower cognitive performance of twins suffering from cardiovascular disease in midlife compared with their healthy co-twins, i.e. strong support for the hypothesis that pathological changes in individuals with cardiovascular diseases do produce memory impairment. Since twin siblings are likely to be similar with respect to heritable traits, discordant twin pairs are rare and we cannot be sure whether other metabolic conditions would have produced significant effects within discordant twin pairs in a larger sample. Indeed, the number of twin pairs discordant with respect to cardiovascular disease was at least 55% higher than those discordant for other metabolic conditions, and a significantly increased risk of dementia in relation to midlife diabetes within discordant pairs was demonstrated in a study population 2.5 times larger than in this study (Xu et al. 2009).

Assuming the  $\beta$ -estimates observed in this study (see Table 3), at least 167 twin pairs discordant for diabetes and 964 discordant for hypertension would have been needed to demonstrate significant  $\beta$ -estimates in the within-pair analyses. Alternatively, clinical observational studies comparing the outcomes of well-treated versus poorly treated metabolic conditions can help to clarify the nature of these associations, since large twin cohorts followed for a long time are rare. Although the Social Insurance Institution's registry records were used in our study, we cannot be sure whether the subjects entitled to reimbursed medication against the metabolic conditions under study had used these medications or not. However, the prevention of and early care for cardiovascular diseases is supported by the results of this study.

## *6.3 Methodological considerations*

### *6.3.1 Assessment of cognition*

Assessing cognition via telephone has some strengths and limitations. In the Finnish sample, a combination of two sensitive and specific telephone screens was used in order to detect subjects having impaired cognition. In the Danish sample, cognitive performance was assessed by using MMSE, a comparable face-to-face interview. It should be noted that high scores in these interviews indicate normal memory, and healthy subjects cannot be rated with respect to each other.

In addition to reliability, financial and time-related aspects must be taken into account in the selection of a cognitive test for screening a large study sample. A higher response and smaller differences between participants and non-participants are expected in a telephone interview, since physical impairment, high travel distances in the countryside and low motivation may reduce the response to face-to-face interviews. In the Finnish cohort, the response rate for the cognitive interview was high (78%), and respondents were comparable to non-respondents (see 4.2.1). For the Danish subjects, cognitive assessment was performed face-to-face and mainly in their homes, which also produced a high response rate (70%).

Although the telephone interview included questions measuring several cognitive domains (see 4.2.1), some cognitive abilities such as visuospatial skills cannot be accurately assessed via telephone. The subjects were advised not to use pens, pencils, papers, newspapers or calendars, but we cannot ensure that they were not used. In addition, hearing problems due to external distractions or impaired hearing may debase the test performance, but a telephone interview can overcome the limitations from visual and upper extremity impairments, unlike the MMSE (Ferrucci et al. 1998).

In a recent family study, telephone administration was not associated with cognitive performance among demented subjects and accounted for less than 1% of the variability in cognitive performance among non-demented subjects, among whom cognitive performance was slightly better when administrated via telephone. The results of the study support the usability of telephone screening in epidemiological investigations. Furthermore, variability in

cognitive performance due to the conducting centre was small relative to the variability due to differences between individuals and families (Wilson et al. 2010). The successful use of telephone screening has been documented in several reports, and a worse performance in Finland, where virtually all residents are reachable via telephone (Figure 15) (Kangassalo 2002), was not expected.

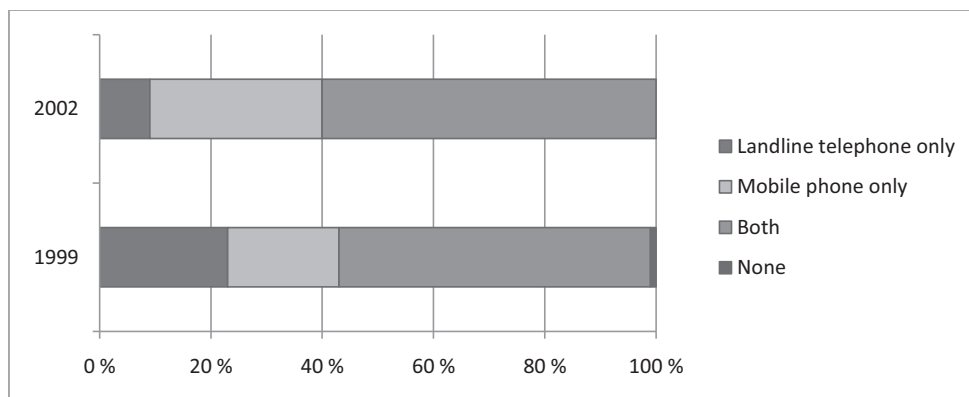


Figure 15. The division of Finnish households on the basis of the telephone at the time of cognitive interview (according to Statistics Finland)

Pearson's correlation coefficients between MMSE and TELE (Pearson's  $r = 0.87$ ,  $p < 0.0001$ ) and TICS (Pearson's  $r = 0.86$ ,  $p < 0.0001$ ) were found to be high in AD patients in this same study population, and the most discriminating questions were orientation to time, the former President of Finland, the 3-word recall and counting backwards from 100 by sevens (Järvenpää et al. 2002), which reflects the impairment of short-term memory, orientation and concentration. However, even higher correlations between MMSE and TELE (Gatz et al. 1995) and TICS (Brandt et al. 1988) have been found in other study populations. Differences in the correlations may reflect differences in the prevalence and distribution of memory disorders between study samples. Thus, the correlation between telephone interview used in the Finnish sample and MMSE used in the Danish sample can be expected to be high, and marked bias due to cognitive administration between the study samples is not expected. Moreover, consistent differences in relation to height are even more unlikely to exist, and the greater variability in the cognitive test results among shorter Finnish subjects, i.e. the main difference between study samples and the basis for performing genetic models among Finnish sample, cannot be explained by differences in the cognitive assessment procedures. Although the Danish subjects were older on an average at the of time cognitive assessment, this is not

likely to reduce the comparability of the study samples, since the potential association between height and cognitive performance would be even more demonstrable in the older sample, and the contradictory finding of this study supports the stronger association between height and cognitive performance among Finnish participants.

Similarly to any cognitive test, better performance in the cognitive telephone test is associated with higher intelligence (Potter et al. 2008) and a higher educational level (Zelinski and Gilewski 2003, Potter et al. 2008,). One study of twins found that intelligence in early adulthood and education accounted for 21% and 17% of the variance in TICS performance in later life. Including both of them and their interaction effect in a multivariate model also explained a slightly greater proportion (25%) of the TICS variance than was explained by the two factors alone and indicated that individuals in the lower range of intellectual aptitude in early adulthood derived greater benefit from an intellectually demanding job (Plassman et al. 1995). In addition, higher intellectual demands and greater interaction and communication at work were associated with a better test performance in TICS, whereas greater physical activity in work was associated with a poorer performance, independently of intelligence and education (Potter et al. 2008). This can be explained by the cognitive reserve theory, i.e. an intellectually demanding job and/or education may increase the capacity to function effectively, even in the context of cognitive decline. However, there is no evidence that these characteristics would have had a greater effect on telephone compared to other cognitive tests. Education, intelligence and work demands are likely to affect both the incidence of memory disorders and the ability to compensate for their manifestations. For instance, people with an advanced education may use more memory strategies, which improves test performance. Thus, it is difficult to estimate the bias due to the latter. However, according to the aforementioned study, about 75% of the variance in TICS performance is due to factors other than education and intelligence in early life (Plassman et al. 1995).

## *6.3.2 Generalization of the results*

### *6.3.2.1 Impaired cognition in relation to dementia*

Dementia is a clinical phenotype that may ensue from several diseases, each of which presents with distinctive pathophysiological and clinical features (see 2.1). Although cognitive impairment is observed in all memory disorders, regardless of their aetiology, it may also result from several other conditions independent of memory disorders. Furthermore, poor performance in a telephone examination may result from various causes (see 6.3.1). In any case, memory disorders cannot be diagnosed via telephone, since this requires accurate physical and mental examination (see 2.1.3).

Since earlier validated cut-off scores were available for clinical categories of impaired cognition, we used them to analyse the effect of the characters under study on the risk for mild impairment of cognitive function and possible dementia. Cut-off score selection was based on receiver operator characteristic (ROC) curves showing the severity of the trade-off between sensitivity and specificity. Cut-off scores for dementia used in our study yielded a sensitivity of 77% and 67% and a specificity of 100% and 96% for TELE and TICS when compared to clinical AD diagnosis in this same study population (Järvenpää et al. 2002). The selection of cut-off scores was made in order to minimize the false-positive rate in the category of possibly demented and false-negative rate in the healthy category. Scores between these indicated mild impairment of cognitive function.

A recent study found a sensitivity of 83% and a specificity of 78% for TICS to differentiate subjects with impaired cognition (MCI and dementia) from the healthy, and a sensitivity of 83% and specificity of 82% for differentiating demented from non-demented subjects, but a misclassification rate of even 57% of MCI subjects if cognition was used as a trichotomous variable, i.e. MCI was included. This indicates a fair performance of TICS when used as a diagnostic tool for MCI compared to good performance for dementia (Knopman et al. 2010). However, the authors highlighted the importance of face-to-face anamnestic interviews and direct patient examinations in order to diagnose MCI. It should be highlighted that in our study, mild impairment of cognitive function was used to describe those who were not classified as either healthy or possibly demented and cannot be compared with MCI which



has accurate diagnostic criteria. Instead, the significantly increased risk for possible dementia and mild impairment of cognitive function in obese and overweight subjects strengthens our study results.

Since the distribution of cognitive scores was approximately normal, the main analyses were performed by using cognition as a continuous variable, which has several advantageous aspects. First, the effect of the characters under study could be examined on the whole range of impaired cognition, not only for possible dementia, which reflects the extreme of cognitive decline. In addition, it was possible to perform genetic modelling to analyse the background of the association between BMI and cognitive scores and the mechanisms underlying the greater variance in cognitive scores among shorter subjects. However, the potential differences in determinants of dementia and cognition as a linear variable should be noted. In particular, the general cognitive ability in elderly can be divided into several domains, each of which shows a different degree of heritability (Lee et al. 2010), whereas in dementia-associated diseases, typical patterns of impairment of cognitive domains are often detected. Thus, at least some differences in the proportions between determinants of general cognitive ability and determinants of specific memory disorders are expected, although some of them, either genetic or environmental, would be the same. Moreover, since dementia always ensues from a pathological process rather than normal aging, some determinants associated with specific diseases and thus present mainly in the lower extremity of cognitive function, are expected.

#### 6.3.2.2 *Twins*

Compared to singletons, twins are smaller at birth. In addition, MZ twins are consistently found to be slightly smaller than DZ twins (Carroll et al. 2005, Gielen et al. 2010), and monozygotic MZ twins are usually smaller than dizygotic MZ twins (Carroll et al. 2005). These differences may reflect the effects of fused placentas and a peripheral cord insertion occurring most frequently in MZ twins (especially monozygotic) (Loos et al. 2005), the chorion type itself (i.e. mono versus dizygotic MZ pregnancy) and/or other factors associated with zygosity. However since maternal intrauterine effects were demonstrated not to be genetically determined (Maes et al. 1997), and genetic differences between twins and

singletons are not expected, these differences are likely to reflect the effect of environmental factors such as restricted intrauterine space and nutrition. Indeed, birth weight increments of twins were found to be close to those for singletons up to about 30 weeks, but diminished progressively during pregnancy from then on (Ananth et al. 1998), possibly reflecting the effect of increasing restrictions in accordance with foetal growth. Moreover, only a little or no deficit in growth of twin newborns was found during the first weeks of their lives, indicating that their early extrauterine growth in weight and height was comparable to that which would have occurred if they had remained with adequate nutrition *in utero* (Buckler and Green 2004).

Since the average gestational age of twins at the time of birth is only 37 weeks, an appropriate comparison of twins with singletons calls for correction of the birth baseline for twins to provide a post-conceptual age of 40 weeks, which is the average gestational age of singletons at birth. Indeed, approximately half of the deviation of SD scores for length and weight from birth until 1.5 years was found to be attributable to gestational age (van Dommelen et al. 2008). However, catch-up growth continues much longer and this growth retardation had reduced to one-third by the age of 2.5 years in a Danish study population (van Dommelen et al. 2008).

At the age of 4 and 5 years, twins were found to have a lower BMI compared to singletons, and though twin girls were as tall as singletons, twin boys were slightly shorter (Buckler and Green 2004, Estourgie-van Burk et al. 2006). However, the height and weight differences between twins and singletons were less than 1 cm and 400 g, respectively (Buckler and Green 2004). A Finnish comparison of twins with 16.5 year-old singletons showed that 17-year-old twin girls were comparable to singletons with respect to both height and BMI, whereas 17-year-old twin boys still had a lower BMI, although they had reached the height of singleton boys (Pietiläinen et al. 1999). However, a Swedish study found that 16- to 25-year-old twin men were still both shorter and lighter than singletons. Nevertheless, the differences in the means were small, since MZ twins were only an average of 0.7 cm shorter and 2.6 kg lighter than singletons, and differences were even smaller between DZ twins and singletons (Silventoinen et al. 2008). In this same study, DZ twins were found to be heavier but not taller than MZ twins, but in some other study populations, DZ twins were found to also be slightly taller than MZ twins (Silventoinen et al. 2003a).

British twin women aged 45-65 years were found to be comparable to singletons with respect to height, and the only difference found in weight was that MZ twins were on average of 2 kg and 2.6 kg lighter and had less variance than DZ twins and singletons (Andrew et al. 2001). Since no substantial differences in body measurements have been demonstrated between adult twins and singletons, twin studies can be used to examine the background of associations with respect to body measurements observed at the population level.

### *6.3.2.3 Self-reports of body measures*

This study was based on self-reports of weight and height. Given the social sensitivity of body images, height is likely to be over-reported, while underreporting of weight, except for the subjects with the lowest BMI, is typical in epidemiological studies among teenagers, adolescents (Fortenberry 1992, Elgar et al. 2005) and adults (Bolton-Smith et al. 2000, Nawaz et al. 2001, Stommel and Schoenborn 2009), especially among the heaviest respondents. The first-mentioned is likely to be more obvious among men, whereas the last-mentioned is more common among women.

Discrepancy between self-reported and physical measures is likely to have a greater impact on the ability to classify subjects into different categories of weight than the use of BMI as a continuous variable. If the standard deviations between self-reported and physical measurements are not large, even substantial misclassifications at the margins of BMI categories would not indicate a low reliability of analyses where BMI is used as a continuous variable, such as in most analyses of this study. Moreover, in this study, no significant discrepancy was detected between self-reports and physical measurements, since a comparison of self-reports of height and weight of 100 men (mean age 52.5 years, SD = 6.5) and 125 women (mean age 50.4 years, SD = 7.9) from the 1990 questionnaire with physical measurements revealed correlations of 0.89 and 0.90 in BMI (Korkeila et al. 1998); for height, these correlations were even higher, i.e. 0.98 in men and 0.96 in women (Silventoinen et al. 2000b). Indeed, underestimates of the actual BMI based on self-reports of body measurements were found to be lowest among 42- to 55-year-old subjects (Stommel and Schoenborn 2009), and another study of subjects aged 25 years or older found that BMI values based on self-reports of height and weight were actually overestimates, except in women aged 55 years or older (Bolton-Smith et al. 2000).

## 7. Conclusions

This study supports the view that cognitive impairment in old age results from the complex interplay between genetic and environmental exposures throughout life. The main attention was focused on environmental exposures whose effect was not clear on the basis of previous studies. Potential determinants under study included midlife coffee drinking, height, BMI, weight change and four metabolic conditions i.e. diabetes, cardiovascular disease, hypertension and hypercholesterolemia. The central role of education was taken into account in this study in addition to several other confounding variables. A genetic approach was taken in order to examine the underlying mechanisms of the correlation between BMI and cognitive performance, and variances in coffee drinking and cognition in old age with respect to height.

This study did not support any independent association between coffee drinking and cognitive decline, and coffee cannot therefore be considered as or recommended to be protective against dementia on the grounds of this study. The large study population and long follow-up period increased the value of the results of this study, whose subjects represented the greatest coffee consuming population in the world. However, since there is stronger evidence of a protective effect of coffee on some other diseases and coffee drinking has an effect on public health, it is important to investigate the determinants of coffee consumption. The heritability of coffee drinking among the Finnish population had not previously been studied, and there had been no previous studies on coffee use in the context of age.

The genetic component influencing coffee drinking was found to explain 51% and 52% of interindividual variance in coffee drinking in men and women. Heritability estimates were highest among younger subjects, whereas middle-age subjects had the highest environmental variance. Both linear and quadratic modification effects of age were observed, and the correlation of coffee drinking between 1975 and 1981 varied between 0.57–0.69, being highest among middle-aged subjects. Genetic factors were stable in all age groups ( $\geq 0.76$ ).

This study demonstrated that higher BMI as a continuous variable and metabolic conditions in midlife, diabetes most of all, were associated with lower cognitive performance in later life. The background to the correlation between BMI and cognition in old age had not been analysed before. This study found evidence of a genetic correlation between these two

variables, although adjustment for education led to a loss of significance, reflecting a strong correlation between education and BMI. Further genetic analysis is needed to reveal the complex interactions between BMI, education and cognition in old age, and whether there is a significant common genetic pathway behind them.

In addition, evidence was found of a direct causal pathway between cardiovascular disease and lower cognitive performance, as inferred using twin data. This highlights the importance of both thorough prevention and the early care of cardiovascular disease. Moreover, a lower degree of weight change than reported previously was found to reduce the cognitive performance.

A comparison of two Nordic study populations revealed a clear and higher decrease in cognitive test performance as a function of decreasing height among Finnish subjects, who had experienced a more restrictive environment during their growth period compared to Danish subjects. Shorter subjects were found to be more vulnerable to environmental factors, whereas the cognitive performance of taller subjects was to a greater extent determined by genetic factors. This suggests that a poor childhood environment may cause wide socioeconomic and public health problems decades later, and the burden of past environmental restrictions may have an influence far into the future. For instance, older birth cohorts in fast developing countries may need more health care in their old age compared to older people of more developed countries. In addition, the results of this study highlight the importance of health and life-style guidance, especially for people who have experienced restrictions in their childhood and their protection from harmful environmental exposures.

This study demonstrated that there is a significant interaction between genes and environmental factors leading cognitive impairment, and demonstrated a substantial set of genes affecting coffee consumption. This is valuable when evaluating whether further efforts to identify genetic and interactive mechanisms are reasonable. Based on this study, further research on genetic responses to environmental exposures associated with cognitive impairment and genetic mechanisms associated with coffee and caffeine preference in different parts of the life cycle can be considered worthwhile. In addition, the findings of this study suggest that the search for genetic mechanisms affecting cognition in old age should be directed elsewhere than genetic pathways involved in BMI determination in adulthood, possibly towards genes involved in educational achievements.

## *7. Acknowledgements*

This study was carried out at the Hjelt Institute, Department of Public Health, University of Helsinki during 2007-2011. I was financially supported by Helsinki Biomedical Graduate School (HBGS) and by Suomen Aivosäätiö Foundation, Kone Foundation and the Finnish Medical Society Duodecim. I do not have a conflict of interest to disclose.

I was responsible for all the analysis and the four manuscripts included in this dissertation, three of which have already been published. I also contributed to the follow-up meetings concerning cognitive and other concomitant examinations for participants of this study and defined the aims of this study together with my instructors.

I was supervised by Professor Jaakko Kaprio and Docent Karri Silventoinen, who picked me up from the 5<sup>th</sup> floor coffee break when I was only a second-year medical student. Jaakko and Karri, I wish to thank you for teaching me everything from the start and introducing me to this fascinating world, in which you both are experts I respect the most. This travel has raised me both as a young researcher and a human being more than I ever expected. Sometimes you believed in me more than I did myself, and that's why I will never forget your support. I am also thankful to other members of our wide research group, and especially to Eila Voipio, the study secretary, and Kauko Heikkilä, the main database manager of our twin group, who has always helped me with all kinds of practical and technical details. The supportive and rousing atmosphere in our group has really inspired me over and over again.

I am very thankful to Professor Markku Koskenvuo from the Department of Public Health, University of Helsinki and my co-workers from the University of Turku: Professor Juha Rinne from the PET centre and Professor Ismo Räihä from the Department of Family Medicine. I really appreciate your time and support during this project. Also, I am thankful to the researchers from the University of Southern Denmark, Odense, with whom I co-worked during the later stage of my project. In particular, I want to thank Professor Kaare Christensen and Associate Professor Jacob Hjelmberg, who worked with me all days during my spring-like stay in Odense in May 2010 and made my time unforgettable with his lovely family.

I wish to express my great gratitude to my thesis committee members, Professor Timo Erkinjuntti from the Department of Neurosciences, University of Helsinki and Docent Tiina Laatikainen from the Chronic Disease Prevention Unit, National Institute for Health and Welfare, both of whom have been level with me during the time of this project and always supported and motivated me in my purposes. Timo and Tiina, I will always be thankful for your time, guidance and support in my research and studies.

From the very beginning, I was supported by the management group of Helsinki Biomedical Graduate School, who noticed my early enthusiasm for entering this fascinating world of medical science and the society of great scientists at the Meilahti campus dedicating themselves to medical purposes, and who supported me financially during the summer periods at medical school. I wish to thank Professor Olli Jänne and other professionals for their time and support for young researchers.

During my graduate education I got to know many great scientists who supported me and taught me many useful clinical skills and shared their medical knowledge with me. In particular, I wish to thank Professors Kaisu Pitkälä and Reijo Tilvis, who led me into the world of geriatric research and practice. Kaisu and Reijo, I will always be thankful to you for showing me how much there is to wonder at the world of aging, and how complicated are the processes underlying the apparently calm clinical phenotypes. In addition, I wish to thank the clinical experts at Laakso City Hospital in Helsinki who introduced me to work with geriatric patients during my first clinical period as a medical doctor, and the experts working in the Alexandroupolis University Hospital in northern Greece for showing me that these problems are universal, although the clinical practices may vary slightly.

I wish to thank associate Professor Miia Kivipelto from University of Eastern Finland and Karolinska Institutet, Sweden, and Professor Ingmar Skoog from University of Gothenburg, Sweden, who pre-reviewed this dissertation and gave me useful tips to improve and clarify my dissertation and to also be used in the future. I thank Roy Siddal from the Language Centre for the linguistic revision of this dissertation and for teaching me linguistic skills during my medical studies.

Last but not least, I wish to thank my family and friends. Above all, I express my gratitude to my lovely mother, who has always been on my side and given me the best advice of my life. I thank my father, sister Veera and grandparents for their love and support. I am deeply indebted to my former teachers who supported me in my studies and thankful to my friends from different parts of life. Finally, this study would not have been possible without the twins participating in this study, thank you!

With great gratitude and love,

*Venla*





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## Telephone Interview for Cognitive Status

### Esitiedot:

- Oletteko juuri nyt virkeä ..... 1 = Kyllä   
0 = Ei
- Kuuluuko hyvin ..... 1 = Kyllä   
0 = Ei
- Käytättekö kuulolaitetta ..... 1 = Kyllä   
0 = Ei
- Oletteko juuri nyt vakinaisessa asuinpaikassanne ..... 1 = Kyllä   
0 = Ei
- Asutteko yksin ..... 1 = Kyllä   
0 = Ei

Muut huomiot \_\_\_\_\_

### Kognitiivista suoriutumista mittavat kysymykset:

1. Mikä on koko nimenne? .....(0-1).....
2. Minkä ikäinen olette nyt / tällä hetkellä? .....(0-1).....
3. Minä vuonna olette syntyneet?.....(0-1).....
4. Monesko päivä olette syntyneet? Mikä kuukausi? .....(0-1).....
5. Monesko päivä on menossa? Entä viikonpäivä ja vuodenaika?
- Monesko päivä?..... (0-1)....
- Mikä kuukausi? ..... (0-1)....
- Mikä vuosi? ..... (0-1)....
- Mikä viikonpäivä? ..... (0-1)....
- Mikä vuodenaika? ..... (0-1)....

6. Painakaa mieleenne seuraavat sanat. Tulen kysymään niitä vielä myöhemmin uudestaan. RUUSU, PALLO, AVAIN. Mitkä sanat sanoin? ..... (0-1).....

7. Vähentäkää luvusta 20 ensin 3 ja tuloksesta uudelleen 3 ja jatkakaa vähentämistä.

Tarvittaessa ohje toistetaan kerran jos tutkittava ei ymmärtänyt tai kuulut ohjetta.

17 ..... (0-0.5)..   
14 ..... (0-0.5)..   
11 ..... (0-0.5)..   
8 ..... (0-0.5)..   
5 ..... (0-0.5)..   
2 ..... (0-0.5)..

8. Kuka on Suomen nykyinen presidentti? .....(0-0.5-1).....   
sekä etu- että sukunimi oikein (1)  
etu- tai sukunimi oikein (0.5)

9. Kuka oli Suomen edellinen presidentti? .....(0-0.5-1).....  
sekä etu- että sukunimi oikein (1)  
etu- tai sukunimi oikein (0.5)

10. Hetki sitten pyysin Teitä painamaan mieleenne kolme sanaa. Voisitteko kertoa, mitkä ne sanat olivat?

RUUSU ..... (0-0.5-1).....  
PALLO ..... (0-0.5-1).....  
AVAIN ..... (0-0.5-1).....

Niiden sanojen kohdalla, joita ei muistettu: Luettelen Teille nyt muutamia sanoja. Sanokaa, minkä niistä mainitsin aikaisemmin.

RUUSU, SORMUS, TUOLI  
HAMMAS, PALLO, OVI  
KYNÄ, PÖYTÄ, AVAIN

11. Mainitsen nyt kaksi asiaa, joilla on keskenään yhtäläisyyksiä. Kertokaa tärkein yhtäläisyys. Esimerkiksi, jos kysytään, mitä yhteistä on koiralla ja leijonalla, oikea vastaus on ”molemmat ovat eläimiä”.

Mitä yhteistä on appelsiinilla ja banaanilla? .....(0-0.5-1).....   
hedelmiä (1)  
ruokia, kumpikin täytyy kuoria, saman värisiä (0.5)  
sisältävät kaloreita, muodoltaan erilaisia (0)

**Mitä yhteistä on pöydällä ja tuolilla?** .....(0-0.5-1).....   
molemmat ovat huonekaluja (1)  
keittiökALUSTEITA, ovat ruokaillessa tarpeellisia (0.5)  
seisovat 4 jalalla, tehty puusta, niillä voi istua (0)

**12. Luetelkaa takaperin numerot 20:stä 0:aan** .....(0-1-2).....   
ensimmäisellä yrityksellä oikein (2)  
toisella yrityksellä oikein (1)  
muuten (0)

**13. Luettelen kymmenen sanaa. Kuunnelkaa tarkasti ja koettakaa muistaa ne. Sen jälkeen luettelkaa niin monta sanaa kuin muistatte. Järjestyksellä ei ole väliä. Sanat ovat**

|  |           |                          |
|--|-----------|--------------------------|
| <input type="checkbox"/> HYTTI .....       | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> PIIPPU .....      | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> ELEFANTTI .....   | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> RINTA .....       | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> SILKKI .....      | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> TEATTERI .....    | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> KELLO .....       | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> RUOSKA .....      | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> TYYNY .....       | (0-1).... | <input type="checkbox"/> |
| <input type="checkbox"/> JÄTTILÄINEN ..... | (0-1).... | <input type="checkbox"/> |

**14. Vähentäkää luvusta 100 ensin 7 ja tuloksesta uudelleen 7 ja jatkakaa vähentämistä (5 kertaa).**

|          |           |                          |
|----------|-----------|--------------------------|
| 93 ..... | (0-1).... | <input type="checkbox"/> |
| 86 ..... | (0-1).... | <input type="checkbox"/> |
| 79 ..... | (0-1).... | <input type="checkbox"/> |
| 72 ..... | (0-1).... | <input type="checkbox"/> |
| 65 ..... | (0-1).... | <input type="checkbox"/> |

**15. Millä yleensä leikataan paperia? Sakset (1).....** (0-1)....

**Kuinka paljon on tusina? 12 (1) .....**(0-1)....

**Mikä on vihreä piikikäs kasvi, joka kasvaa autiomaassa? Kaktus (1) .....**(0-1)....

**Mistä eläimestä saadaan villaa? Lammas (1) .....**(0-1)....

**16. Seuraavaksi luen pari lausetta. Toistakaa lauseet sanatarkasti**

(onnistuttava täysin oikein ensimmäisellä kerralla):

OPPILAS RATKAISI MONIMUTKAISEN TEHTÄVÄN .....(0-1)....

**Ja sitten toinen lause:**

EI MITÄÄN MUTTIA EIKÄ JOSSITTELUA.....(0-1)....

**17. Seuraavaksi pyydän Teitä koputtamaan sormella viisi kertaa puhelimen**

**siihen osaan, mihin puhutaan** .....(0-1-2).....

viisi koputusta (2)

enemmän tai vähemmän kuin viisi koputusta (1)

ei koputuksia (0)

**18. Sanon sanan ja Teidän pitäisi keksiä sille vastakohta. Esim. kuuman vastakohta on kylmä.**

**Mikä on vastakohta sanalle länsi? itä (1)** .....(0-1)....

**Mikä on anteliaan vastakohta? saita itara tai muu vastaava (1)** .....(0-1)....

**19. Luetelkaa minuutin aikana niin monta eläintä kuin tulee mieleen (N)**.....

**20. Missä olette juuri nyt?**

katu/tie..... (0-1)....

kaupunki/kunta..... (0-1)....

postinumero ..... (0-1)....

lääni ..... (0-1)....

**Terveydentilaa kartoittavat kysymykset:**

**( myös omaiselta/huoltajalta, jos tällainen on läsnä)**

**Kysymykset 21 -24** 0 = en

1 = kyllä, mutta tarvitsen toisen  
henkilön apua

2 = kyllä, en tarvitse apua

**21. Hoidatteko itse taloutenne?** .....

**22. Pystyttekö liikkumaan ulkona?** .....

23. Käyttekö itse kaupassa? .....

24. Kykenettekö pukeutumaan ja riisuutumaan itse? .....

Kysymykset 25 -28 0 = ei  
1 = kyllä

25. Käytättekö apuvälineitä liikkuessanne? .....

26. Esiintyykö Teillä vaikeuksia muistaa asioita? .....

27. Oletteko ollut lääkärin tutkimuksissa muistivaikeuksien vuoksi? .....

28. Käytättekö lääkkeitä johonkin seuraavista sairauksista:

verenpainetauti .....

sokeritauti.....

korkea kolesteroli.....

sepelvaltimotauti/sydänveritulppa.....

sydämen vajaatoiminta.....

eteisvärinä.....

aivoverenkiertohäiriö/halvauksen jälkitila.....

muistihäiriö/dementia .....

Parkinsonin tauti .....

epilepsia .....

masennus/alakuloisuus .....

nivelreuma .....

vaikea nivelkuluma / (nivelrikko) .....

29. Onko Teillä muita säännöllisesti käytettäviä lääkkeitä?

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.....  
.....

