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Body Mass Index, Cognitive Ability, and Dementia

Prospective Associations and Methodological Issues in Late Life

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Abstract

The aims of the present study were to investigate the association between overweight and cognitive ability and dementia, and to evaluate the usefulness of self-reported body mass index (BMI) in late life and various data sources commonly used in epidemiological studies to identify persons with dementia. Data were drawn from three population-based studies: the Swedish Adoption/Twin Study of Aging (SATSA), Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behaviour and Health among Elderly (the Gender Study), and the Finnish Lieto Study. In **Study I**, the agreement between self-reported and measured BMI over time was evaluated among 774 men and women, ages 40 to 88 years at baseline (mean age 63.9) participating in both the questionnaire phase and in-person testing of SATSA. Latent growth curve (LGC) modeling showed a small but significant increase between self-reported and measured BMI (0.02 $kg/m^2/y$) over time, which would probably not affect the results if self-reported BMI were used as a continuous variable in longitudinal research. In **Study II**, the agreement between dementia diagnoses from various sources and dementia diagnoses set at a consensus conference was evaluated. Among the 498 elderly people ages 70 to 81 at baseline (mean age 74.5) enrolled in the Gender Study, 87 were diagnosed with dementia during an eight-year period. Review of medical records and nurse evaluations yielded the highest sensitivity (0.83 and 0.80, respectively) and a high specificity (0.98 and 0.96), indicating that these sources might be good proxies of dementia, while data extraction from the Swedish Inpatient Discharge Registry underestimated the prevalence of dementia (sensitivity 0.26). In **Study III**, the association between being overweight in midlife and cognitive ability in late life was examined in SATSA. The 781 participants ages 25 to 63 at baseline (mean age 41.6) in 1963 or 1973 self-reported their height and weight. From 1986 until 2002, they were assessed five times using a cognitive test battery. LGC models showed that people with higher midlife BMI scores had significantly lower cognitive ability and a significantly steeper decline than their thinner counterparts, an association that persisted when those who developed dementia during the study period were excluded from the analysis. This finding indicates that being overweight might affect cognitive ability independently of dementia. In **Study IV**, the association between BMI and dementia risk in older persons was described among 605 persons without dementia and ages 65 to 92 at baseline (mean age 70.8) in the Lieto Study. Among these, 86 persons were diagnosed with dementia during eight years of follow-up. Cox regression analyses indicated that for each unit increase in BMI score, the risk of dementia decreased 8% (hazard ratio = 0.92, 95% confidence interval = 0.87–0.97) and the association remained significant when individuals who developed dementia during the first four years of follow-up were excluded from the analyses. This result suggests that low BMI scores are present almost a decade before clinical dementia onset.

Swedish abstract

Syftet med den här studien är att studera sambandet mellan övervikt, kognitiv funktion och demens, och att bedöma tillförlitligheten av självrapporterat body mass index (BMI) och olika datakällor som ofta används i epidemiologiska studier för att identifiera personer med demens. I avhandlingen används data från tre populationsbaserade studier: the Swedish Adoption/Twin Study of Aging (SATSA), Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behaviour and Health among Elderly (Gender studien) och den Finska Lieto studien. I **studie I** granskas överensstämmelsen mellan självrapporterad och uppmätt BMI bland 774 män och kvinnor i SATSA, 40 till 88 år (medelålder 63.9 år) vid det första mättillfället. Latent growth curve (LGC) modeller visade en liten men signifikant ökning i medelvärdesskillnaden mellan uppmätt och självrapporterat BMI (0.02 kg/m^2/år) över tid, som förmodligen inte påverkar resultaten om BMI används som en kontinuerlig variabel i longitudinella studier. I **studie II** utvärderas överensstämmelsen mellan demensdiagnoser från en konsensuskonferens med demensdiagnoser från andra källor. Av 498 personer som var 70 till 81 år vid det första mättillfället (medelålder 74.5 år) i Gender studien diagnostiserades 87 personer med demens under de åtta år som studien pågick. De bästa datakällorna var de medicinska journalerna och sjuksköterskornas bedömningar, med både hög sensitivitet (0.83 och 0.80) och specificitet (0.98 och 0.96). Sensitiviteten för slutenvårdsregistret var låg (0.26) och underestimerade därmed prevalensen av demens. I **studie III** analyseras sambandet mellan övervikt i medelåldern och kognitiv förmåga i hög ålder. De 781 personer som deltog i SATSA var 25 till 63 år vid det första mättillfället (medelålder 41.6 år) 1963 eller 1973, då de självrapporterade längd och vikt. Med start 1986 testades dessa personers kognitiva förmåga fem gånger fram till och med 2002. LGC-modeller visade att personer som var överviktiga i medelåldern hade lägre kognitiv förmåga och att den förmågan försämrades snabbare i hög ålder, även när personer med demens uteslöts från analyserna, vilket tyder på att övervikt i medelåldern påverkar den kognitiva förmågan oberoende av demens. I **studie IV** studeras sambandet mellan BMI och demensrisk bland 605 personer som var 65 till 92 år vid första mättillfället (medelålder 70.8 år) i Lieto studien. Bland dessa diagnostiserades 86 personer med demens under en uppföljningsperiod på åtta år. Cox regressioner visade att för varje enhetsökning i BMI minskade risken att drabbas av demens med åtta procent (hazard ratio=0.92, 95% konfidensintervall=0.87–0.97). Sambandet kvarstod då personer som diagnostiserades med demens under de först fyra åren uteslöts från analyserna, vilket tyder på att personer som drabbas av demens har ett lågt BMI minst åtta år innan demens konstateras kliniskt.

Original papers

The thesis is based on the following papers, referred to in the text by their Roman numerals:

I. Dahl, A., Hassing, L.B., Fransson, E. & Pedersen, N.L. Agreement between Self-reported and Measured Height, Weight, and Body Mass Index in Old Age – a Longitudinal Study with 20 Years of Follow-up. Submitted.

II. Dahl, A., Berg, S. & Nilsson, S. Identification of Dementia in Epidemiological Research – a Study of the Usefulness of Various Data Sources. Aging Clinical and Experimental Research 2007;19:381-389.

III. Dahl, A., Hassing, L.B., Fransson, E., Berg, S., Gatz, M., Reynolds, C.A. & Pedersen, N.L. Being Overweight in Midlife Is Associated with Lower Cognitive Ability and Steeper Cognitive Decline in Late Life. Journal of Gerontology A Biological Sciences Medical Sciences doi:10.1093/Gerona/glp035.

IV. Dahl. A., Löppönen, M., Isoaho, R., Berg, S. & Kivelä, S-L. Overweight and Obesity in Old Age Are Not Associated with Greater Dementia Risk. Journal of American Geriatric Society 2008; 56:2261-2266.

Abbreviations

AD	Alzheimer's disease
APOE	Apolipoprotein E gene
ATC	Anatomical therapeutic chemical classification system
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
Gender Study	Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behaviour and Health among Elderly
ECG	Electrocardiograms
HR	Hazard ratio
ICD-10	International Statistical Classification of Disease and Related Health Problems, version 10
IDR	In-patient discharge registry
IPT	In-person testing
MCI	Mild cognitive impairment
MetS	Metabolic syndrome
MMSE	Mini-Mental State Examination
NPV	Negative predictive value
NSAID	Nonsteroidal anti-inflammatory drugs
PPV	Positive predictive value
SATSA	Swedish Adoption/Twin Study of Aging
sCRP	Serum C-reactive protein
STR	Swedish Twin Registry
SD	Standard deviation
WHO	World Health Organization
VaD	Vascular dementia

Contents

1. Introduction

1.1. Background

Maintaining cognitive functioning in late life is essential for independence, health, quality of life, and survival. A better understanding of the factors that contribute to maintaining cognitive functioning in late life is important for the individual but also for society at large. Despite the acknowledged significant genetic contribution to cognitive functioning[1] and dementia,[2] a growing body of evidence indicates that environmental influence on cognitive functioning is greater in late life than at younger ages.[3-6] Additionally, environmental factors affect the rate of change in cognitive functioning more than the variation in mean level performance.[6,7] In other words, cognitive decline in late life is partly attributable to health and lifestyle factors, which might be modifiable. Among the various risk factors that can be studied, we considered overweight and obesity to be of particular interest.

1.2. Overweight and Obesity

According to the World Health Organization (WHO), excess body weight is a global health problem that has reached epidemic proportions.[8] More than 50% of the U.S. and European adult populations are overweight or obese.[9,10] Excess body weight is among the most significant contributors to ill health, both independently and in association with other diseases.[8,11] Specifically, excess body weight is associated with an increased risk of cardiovascular disease (CVD) and metabolic disorders such as diabetes mellitus.

1.2.1. Body Mass Index

Body fat is usually assessed with anthropometric measures, such as body mass index (BMI), waist circumference, waist–hip ratio, and skinfold thickness. BMI is calculated as weight in kilograms divided by height in meters squared. The underlying assumption of BMI as a measure of adiposity is that most of the

variation in weight is due to fat mass. Though BMI does not differentiate between fat and muscle, it is strongly correlated with total body fat.[12,13] However, it should be kept in mind that a BMI score does not always correspond to the same degree of fatness across various populations, depending on ethnicity, gender, and age.[11-14] To categorize and interpret the risk associated with excess body fat, BMI is classified into four different categories: underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obese (BMI ≥ 30.0).[15] Both overweight and obesity are associated with increased health risks, and obesity is defined as a state in which excess body fat has accumulated to affect health in a negative way.[11] Even though these BMI categories are well established, it should be remembered that fatness is a continuum and in general the risk of negative health consequences increases with each BMI unit. Because the studies reviewed in this thesis used BMI both as a continuous variable and as a categorical variable with different cut-offs, the term "overweight" is used as a collective designation for BMI scores above 25, i.e., it includes persons who are obese. Overweight is also used as the term for excess weight in the general discussion, while more specific terms are used when they might be of interest for the reader.

Accuracy of Self-reported Body Mass Index

In epidemiological studies, BMI values are often based on self-reported weight and height, anthropometric measures that people in general know fairly accurately compared to waist circumference, waist–hip ratio, or skinfold thickness. Accordingly, the correlation between self-reported and measured height, weight, and BMI is in general high.[16-20] Young and middle-aged individuals tend to under-report their weight by up to 2.5 kg,[18,21-23] and over-report their height by about 1 cm,[18,22,23] leading to an underestimation of their actual BMI. In general, persons who are overweight underestimate their BMI more than persons who are normal weight, and women underestimate their BMI more than men.

The aging process is accompanied by changes in body composition such as a decline in stature. It has been proposed that self-reported BMI is less reliable in old age than for younger age groups because of a lack of awareness of these changes.[18,22] Memory problems might also make self-report less reliable in old age. Others have suggested that self-report is more reliable in old age because there is less social pressure to be thin.[24] Cross-sectional studies have shown that there is more misclassification of height among older adults compared with younger adults,[17,18,22,23,25] with older persons being more likely than younger persons to overestimate their height. The results are less clear concerning weight. In the U.S. second and third National Health and Nutrition Examination Survey,[18,22,25] women as a whole underestimated their weight, but older women more accurately reported their weight than their younger counterparts.[18,25] This pattern was also seen among obese elderly women.[22] Men, on the other hand, as a whole overestimated their weight, with the highest overestimation seen in the oldest age group (80 years and above). In a Swedish study including both men and women, elderly (65–84 years) overweight and obese persons reported their weight with greater accuracy than younger overweight and obese persons.[23]

Overall, previous studies including various age groups have found that self-reported BMI is less reliable in old age compared with self-reported BMI in young age.[18,23,25-27] However, because of the cross-sectional design in these studies, it is not possible to draw any conclusions about whether these age differences arise from inter-individual differences like cohort differences or intra-individual changes. Studies with a longitudinal design can overcome this limitation.

1.3. Cognitive Abilities and Cognitive Decline

Cognitive psychology is the study of internal mental processes like memory and thinking abilities. The goal is to identify, measure, and distinguish between abilities that underlie the complex nature of thinking and the processing of information. It has been suggested that there are a hundred or more different cognitive abilities;

however, most researchers believe that the number is less. Memory, verbal abilities, spatial abilities, and processing speed are some abilities that are considered to be distinct. It is also generally accepted that there are two general intelligences, fluid and crystallized intelligence.[28] Fluid intelligence is defined as the ability to solve problems with novel material, in which a person's earlier experience does not help or provide a solution. This problem solving relies on reasoning and logical and abstract thinking and the capacity of the short-term memory. Crystallized intelligence, on the other hand, applies previously learned material for problem solving; thus, the ability to retrieve stored information from the long-term memory is important. Despite distinct features of various cognitive abilities, it is also generally considered that there is a general intelligence factor, often referred to as the *g* factor, that contributes to the variance in each cognitive ability. This factor is usually derived from all cognitive tests included in a test battery. The concept of cognitive decline is generally and in this thesis defined as a decreased score on measures of cognitive abilities, not related to dementia but to age.

1.3.1. Cognitive Aging

Even though elderly people often complain about cognitive problems, like finding words and/or remembering names and faces, the decline in cognitive abilities seen during normal aging is quite small and does not affect the older person's ability to remain independent. However, there are large intra-individual differences: Some people show a steep decline, some stay fairly constant, and some even improve,[29,30] as Figure 1 illustrates. On average, cognitive test performance remains stable through adulthood and starts to decline around the age of 65.[31] The decline accelerates before

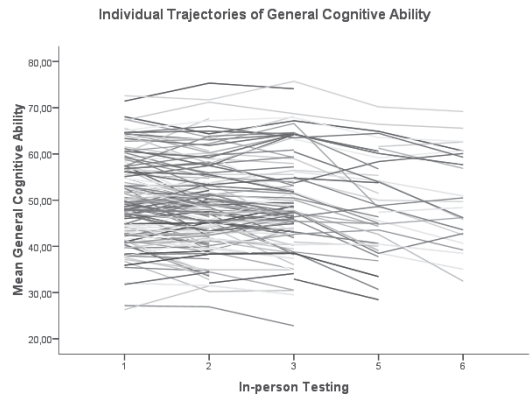

Figure 1. Person-specific Trajectories of Change in General Cognitive Ability.

death,[32] and some cognitive abilities are more age sensitive than others; in general, fluid abilities are considered to be more age sensitive than crystallized abilities like verbal abilities.[28] The final drop in cognitive performance is often referred to as a terminal decline or terminal drop. The length of the terminal decline phase varies between cognitive domains.[32]

1.4. Dementia

The main threat to retaining cognitive functioning in old age is dementia, but the border between normal cognitive aging and dementia is blurry. A transitional step between normal cognitive aging and dementia is mild cognitive impairment (MCI). Symptoms like memory problems and deficits in attention are common but not severe enough to particularly interfere with activities of daily living.[33] About 15% of people over age 65 years are estimated to be affected by MCI,[34] and among these, about 10–30% have developed dementia within two years.[35]

The prevalence of dementia is estimated to be at least 6% to 10% among persons 65 years and above.[36] The most widely used dementia criteria are those given in the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV).[37] A person is diagnosed with dementia if there is a gradual and progressive decline in memory; impairment in at least one other cognitive function such as agnosia, aphasia, or apraxia; and/or a disturbance in executive functioning. These disturbances must also lead to the inability to manage daily living.[37] Changes in personality and behavioral disturbances are also common symptoms of dementia but are not required criteria according to the DSM-IV. Other diseases or states causing dementia-like symptoms, such as depression and confusion, should preferably be excluded before a dementia diagnosis is made.

The most common type of dementia is Alzheimer's disease (AD) followed by vascular dementia (VaD). Less common forms of dementia include Lewy body dementia, frontal lobe dementia, and dementias arising from secondary causes like

trauma or tumors. AD accounts for about 50–70% of all dementia cases,[34,38] and its hallmark is the accumulation of amyloid β in the brain that causes synapse disruption and neuronal death. VaD accounts for about 20–30% of all dementia cases.[38] It is a heterogeneous disorder caused by cerebrovascular complications ranging from small vessel ischemic disease to stroke. There is a great overlap between AD and VaD, resulting in a condition often referred to as mixed dementia.[39] Indeed, the two also may be related: AD pathology has been proposed to increase the risk of vascular injury and vice versa.[40]

1.4.1. Diagnosing Dementia

In clinical practice, identification of dementia is of major importance. Recognizing dementia can enhance safety in such situations as medication use and driving. Early diagnosis also allows the patient and family to plan for the future while the ability to make decisions remains. In addition, AD medications are thought to be most effective in the early course of the disease, another reason that early and correct diagnosis is so important. In research, the validity of dementia diagnosis is critical, not least in studies of risk factors in which over- or underestimations might blur the association.

Diagnosing dementia is tricky, both in clinical practice and research, because there is no single hallmark and symptoms in the preclinical phase can be diffuse and insidious. A wide range of physical tests, including blood sampling and cognitive evaluations, are considered the cornerstones of diagnosis together with careful consideration of the patient's medical history. Brain imaging and analyses of spinal fluid give additional information. An extensive clinical work-up is the gold standard in dementia diagnosis; however, in epidemiological studies, clinical examination is not always possible because of a lack of financial resources and/or time. Thus, methods that are less costly and time consuming serve as proxies of dementia. Little is known about the precision of these proxies, despite their common use.

The accurate identification of dementia by medical records review depends on the physician's knowledge and willingness to evaluate cognitive impairments as well as to record them. Two studies of data collected in the beginning of the 1990s, one from Sweden and one from the United States, reported low identification rates,[41,42] whereas three more recent studies, one from Finland and two from the United States, report higher identification rates.[43-45] In this latter group of studies, about 70–80% of the people with dementia were identified as being cognitively impaired or were diagnosed with dementia by their physician.

Nurses make up another group of medical care staff having frequent contact with persons with dementia. To our knowledge, the accuracy of nurse recognition of dementia in a real setting has not been researched, even though nurses might be well positioned in both research and clinical practice to first note cognitive changes, often seeing participants or patients more frequently for longer periods than physicians do.

Because cognitive impairment is a major symptom of dementia, cognitive testing is commonly used both for screening and diagnosing. The most commonly used screening test is the Mini-Mental State Examination (MMSE),[46] whereas extended cognitive testing is frequently used for screening for differential diagnoses. The shortcomings of the MMSE are well known and include insensitivity to detecting small cognitive changes and a bias against older people and those with lower levels of education. Nevertheless, the test is considered a good proxy of moderate and severe dementia.[47] Appropriate cut-off scores for various cognitive tests are unknown because so many are in use and constantly being developed. To overcome this lack of consistency, cut-off scores at the 10th percentile have been suggested as a good proxy of dementia in epidemiological research if no standardized cut-off scores are available.[48] Several cognitive tests considered together ought to give a more accurate picture of a person's cognitive status. Accordingly, a study from the Monongahela Valley Independent Elders Survey shows that a cognitive test battery is more sensitive than the MMSE for identifying dementia,[48] while another study

from the same sample showed that the MMSE is as effective as the cognitive test battery in distinguishing dementia.[49]

Retrieval from population-based disease registers is becoming a more common data collection method, probably because it is a time- and money-saving assessment method, yet little is known about its reliability in identifying persons diagnosed with dementia. One earlier population-based study showed that the agreement between the consensus diagnosis and the Swedish Inpatient Discharge Registry (IDR) was better for prevalence of dementia cases than for incidence cases;[50] about one out of two persons diagnosed with dementia appeared in the registry. The fit improved with the addition of information from the cause-of-death registry. In a study from Italy, less than 50% of the persons with a dementia diagnosis were identified by a dementia registry, and older persons with dementia were less likely to have been registered as a person with dementia in the registry.[51]

1.5. Risk and Protective Factors of Cognitive Decline and Dementia

A number of factors have been proposed to contribute to cognitive decline and dementia in late life, ranging from biological factors like age and gender to television watching. The level of evidence for the contribution of various risk and protective factors also ranges from very strong to very weak. Most studies have quite short follow-up times, ranging from a couple of years to 10 years; studies with longer follow-up times are less common. The time of assessment and the follow-up time are important because the preclinical dementia phase, including changes in cognitive abilities and metabolism, is considered to start at least 10 years before clinical onset.[52-54] Hence, in studies of risk factors of dementia in late life, preclinical phases might blur conclusions about causality. Preclinical phases are less likely to affect results of studies assessing risk and protective factors in early life and/or midlife, when cognitive decline and dementia are uncommon, and such studies might give a more accurate indication of causality.

Genes

A family history of dementia is one of the strongest risk factors for dementia. However, few genetic mutations with a definite association have been identified, except for those in genes encoding amyloid precursor protein, Presenilin 1, and Presenelin 2.[55] These gene changes, associated with early onset AD, account for a small number of all cases of AD, about 2–3%. The apolipoprotein (APOE) ε4 allele is a well-established risk factor for AD but also for cognitive decline.[56] A NOTCH 3 mutation is considered to be associated with VaD.[57] The influence of genes on cognitive functioning is well established; among young and middle-aged adults, genetic factors are estimated to account for about 50% to 80% of the variance in cognitive test performance,[1,58] but over the life span, the importance of genes seems to decrease substantially.[3-6] Moreover, the genetic contribution in old age seems to be primarily to variation at the mean level, while the variation in the trajectories seems to be attributable to a larger environmental component.[4-6] Likewise, the effect of APOE ε4 on dementia risk decreases with increasing age.[59] These findings stress the importance of understanding which modifiable lifestyle factors contribute to cognitive decline and dementia in late life.

Biological Factors

The risk of dementia increases with increasing age. At age 65 years, about 1% of the population is diagnosed with dementia, whereas by age 85, the frequency has increased to 25%,[60] and after age 90, about 50% of this age group is considered to be cognitively impaired or to have a dementia diagnosis.[61,62] However, among the oldest elderly, the incidence rates of dementia are suggested to slow down[63,64] or even flatten.[65] This shift suggests that dementia might rather be a state occurring more commonly in specific age ranges than a state caused by the aging process.[65] In other words, dementia might not be inevitable in old age. Female gender is associated with a higher risk of AD,[63,66] while it has been suggested that VaD is more common among men,[64] although this association is not conclusive.[66]

Vascular Factors

Various review articles link stroke, coronary artery disease, and congestive heart failure with an increased risk of cognitive decline and dementia in late life.[67,68] Hypertension,[69,70] diabetes mellitus,[71-74] and hyperlipidemia[75] in midlife are among the most well-established risk factors for cognitive decline and dementia. Accordingly, the use of antihypertensive[70] and lipid-lowering medications[76] and better glycemic control are proposed to have a protective effect against dementia.[77] The clustering of overweight and especially central obesity, hypertension, hyperlipidemia, and insulin resistance and/or type 2 diabetes is often referred to as the metabolic syndrome (MetS),[78] which also has been linked to an increased risk of dementia, especially dementia of vascular origin.[79] Serum C-reactive protein (sCRP) is a nonspecific inflammation marker that has been suggested to have a central role in the pathogenesis of atherosclerosis, or at least being a underlying marker, and that has been associated with cognitive decline[80,81] and increased risk of dementia.[82] Further support for the association between inflammation and lower cognitive abilities is that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to lower the risk of dementia and cognitive decline, especially if the use begins in midlife and continues over an extended period of time.[83-85]

Lifestyle Factors

The most researched lifestyle factor in relation to cognitive decline and dementia is education: less education has been associated with both an increased risk of cognitive decline[86] and dementia.[87,88] Interrelated with education are socioeconomic status and occupation, where higher socioeconomic status,[89] and stimulating work[90,91] are associated with a decreased risk of cognitive decline and dementia. A rich social network[92] and mentally stimulating leisure activities[93,94] are proposed to be protective, but results of randomized controlled trials in older age groups do not always support the notion that cognitive stimulation is protective against cognitive decline and dementia.[95] Alcohol consumption (both heavy drinking and abstaining),[96] cigarette smoking,[97] and a sedentary lifestyle (i.e., absence of exercise)[98-100] have been associated with an increased risk of cognitive decline and dementia. Available data on dietary habits and brain functioning are still

inconclusive and scarce.[101] However, it is well established that vitamin B12 and/or folic acid deficiency (sometimes indicated by high levels of homocysteine) are associated with cognitive decline and dementia.[102,103] Among other proposed factors, healthy dietary habits like fish consumption and a higher intake of fruits and vegetables have been associated with better brain functioning,[104-106] and a high intake of fat has been associated with lower brain functioning.[107,108]

1.5.1. Overweight and Brain Functioning

Overweight in Midlife and Risk of Dementia

As highlighted in several reviews,[109-111] an increasing body of evidence links overweight in midlife with dementia[79,112-117] and with temporal atrophy,[118] which might be an early marker of cerebral degeneration and neuronal death. Most studies link overweight in midlife to an increased risk of both AD and VaD,[114,117,119] except for the U.S. Cardiovascular Health Study, which found that obesity in midlife was associated only with an increased risk of VaD but not with AD.[120] Studies including measures of adiposity other than BMI indicate that persons carrying abdominal fat are especially at a greater risk of dementia.[112,115] On the other hand, being thin in midlife is not always beneficial, either. Two studies report a U-shaped association between midlife BMI and dementia in late life.[112,116] In studies that have addressed gender differences, some report that the association between higher midlife BMI and an increased risk of AD are stronger for women than men,[112,114] whereas others found no gender differences.[117]

It has been suggested that CVDs and related states could be on the causal pathway between overweight and an increased dementia risk because overweight is correlated with CVDs, which in turn have been associated with an increased dementia risk, especially of vascular origin. However, previous findings are inconclusive. In some studies, the association between midlife overweight and all-cause dementia is attenuated or becomes non-significant when controlled for CVD and related states,[119,120] while CVD does not seem to affect the association in other studies.[116,117] In the Kaiser Permanente Study, the association became even stronger when CVDs

were controlled for.[113] However, studying only the association between BMI and all-cause dementia might be misleading because the pathological processes linking midlife overweight to VaD and AD might differ. In a study from the Swedish Twin Registry (STR), the association between midlife overweight and an increased risk of dementia became non-significant relative to VaD when CVDs and associated states were controlled for, but not to AD.[117] Likewise, the association between obesity and VaD was no longer significant when CVDs were controlled for in the Cardiovascular Health Study.[120] However, in the Finnish Cardiovascular Risk Factors and Dementia Study, the association between midlife overweight and increased risk of AD was attenuated and became non-significant when CVDs and related states were controlled for.[119]

Overweight in Midlife and Cognitive Abilities in Late Life

Knowledge about the association between midlife overweight and prospective cognitive functioning is scarce. In the Whitehall II Study, young elderly persons who were either underweight or obese in midlife had an increased risk of lower cognitive functioning (mean age 61 years).[121] Specifically, midlife underweight was associated with lower executive function and midlife obesity with lower scores on the MMSE and tests of memory and executive abilities. In the Framingham Offspring Study sample (age 40–69 years at baseline), midlife obesity was related to poor performance on tests of executive functioning and spatial abilities about 10 years later.[122] Even though the participants in these study samples could be considered as young elderly at the time of cognitive function assessment, the association between midlife BMI and lower executive functioning and memory performance in these studies might still represent an association between midlife BMI and dementia; the prevalence of dementia was not controlled for. Both deficits in executive functioning and memory are often noticed early in the preclinical states of dementia.[123]

Overweight in Late Life and Dementia Risk

The study of risk factors of dementia in late life is more complicated than assessment of risk factors in midlife. In late life, risk factors might no longer be risk

factors but instead be preclinical features of dementia. As already mentioned, changes can be seen at least a decade before the clinical onset of dementia. Bearing this in mind, it might not be surprising that weight loss and low weight precedes AD,[124] VaD,[125] all-cause dementia,[126,127] and dementia associated with stroke,[127] and that concordantly declining BMI and/or low BMI scores in late life are associated with an increased risk of AD,[120,125,128-130] VaD,[120,125] and all-cause dementia.[120,127,130-133] Weight loss is a well-known clinical feature of persons with dementia. On the other hand, high BMI scores in old age have also been associated with greater risk of AD,[134,135] and one study reports a U-shaped association between BMI scores and all-cause dementia.[127] Overall, most studies show that high BMI scores in midlife are associated with a greater dementia risk, while the opposite is mainly seen in late life, especially in studies with shorter follow-up. This conclusion was confirmed in the Cardiovascular Health Study, which followed one cohort from midlife to late life with subsequent assessments of BMI.[120]

Women have a significantly greater amount of total body fat than men for an equivalent BMI;[12,13] hence, analyses of BMI should preferably be stratified according to gender. Most studies on BMI in late life and risk of dementia have not evaluated or reported gender differences,[125,127-129,132] and among studies that have done so, results conflict. The Cache County Study reported that high BMI scores in late life increased the risk of AD in women but not in men.[135] In the Rochester Epidemiology Project, women diagnosed with dementia weighed less 11–20 years before the clinical manifestation of dementia than their cognitively intact counterparts.[126] There was no such association between weight and future dementia in men in that study. In contrast, in the H70 study, women who developed AD had higher BMI scores at baseline (no analysis was performed on men),[134] and in the Rancho Bernardo Study, men weighed slightly more 20 years before AD onset, while there was no difference for women.[136] Data from the Sacramento Area Latino Study showed that low BMI was associated with greater dementia risk among both men and women.[133]

To try to overcome the shortcomings of BMI, studies in recent years have also included and evaluated the association between other measures of adiposity and dementia risk, but so far, this work has not made the picture clearer. A greater waist circumference in late life has been associated with a decreased risk of AD and overall dementia over a four-year period[137] but also with a greater risk of dementia and dementia associated with stroke over five to eight years.[127,133] In two other studies, waist–hip ratio and waist circumference were not associated with either higher or lower risk of dementia of any origin over seven years.[120,130]

The main threat to retaining cognitive abilities in late life is dementia. Accordingly, if the interest is in normal cognitive aging, any person diagnosed with dementia should preferably be excluded from such studies. To our knowledge, none of the studies described below have done so. Thus, in the interpretation of the following results regarding associations between late-life BMI and cognitive abilities, it should be kept in mind that the cognitive changes observed might be due to dementia and not to cognitive aging *per se*.

In the Basel Study, either an increase or a decrease in BMI over a 10-year period negatively affected general cognitive ability.[138] Persons who maintained their weight were those most likely not to be cognitively impaired. In the Religious Order Study, those with increasing BMI scores and/or those with high BMI scores were the ones who performed better on a composite score of cognitive functioning.[129] Additionally, women who had the lowest central fat mass at baseline and lost the most weight from baseline to follow-up in the Prospective Epidemiological Risk Factor Study had the lowest cognitive test performance on a test of memory, orientation, and concentration at follow-up nine years later.[139] In the Framingham Heart Study, elderly obese men had an increased risk of lower performance on a global composite score 18 years after entry compared to non-obese men.[140,141] However, this association was not observed among women. Likewise, in the Health, Aging, and Body Composition Study, in which adiposity was assessed with various anthropometric measures, excess fat was associated with declining cognitive ability

over a seven-year period in men, whereas excess fat tended to be associated with less cognitive decline in women.[142]

In summary, although a growing number of studies focus on the association between overweight and brain health, the knowledge is still scarce, with previous studies producing contradictory findings and/or containing methodological limitations. The current analyses test the accuracy of self-reported BMI and various assessment methods of dementia, commonly used in this research field, to achieve a better understanding of the reliability of these variables. By evaluating the long-term association between midlife BMI and late-life change in cognitive ability as well as the association between late life BMI and dementia, this thesis will clarify and expand knowledge beyond previous findings, taking different time spans and age groups into consideration. We also try to overcome some of the methodological limitations of previous studies, for example, by excluding persons with dementia when the association between midlife BMI and cognitive ability in late life is studied. Exploring the association between BMI and brain health controlling for variables that might be on the causal pathways, will likely led to a better understanding of which mechanisms contribute to neurodegeneration.

2. Aims of the Study

The overall aim of the present study was to assess the association between overweight and cognitive ability and dementia, and to evaluate the usefulness of self-reported BMI in late life and various data sources commonly used in epidemiological studies to identify persons with dementia.

Specific aims:

I. To evaluate the accuracy of self-reported height, weight, and BMI (based on self-reported height and weight) longitudinally in old age and to evaluate if the reliability is influenced by gender, BMI, or prevalence of dementia.

II. To evaluate the agreement between dementia diagnoses made at a consensus conference from an extensive test protocol with up to three measurement occasions and dementia diagnoses derived from medical records review, the Swedish discharge registry, separate cognitive tests, a cognitive test battery, and nurse evaluations.

III. To describe the association between midlife BMI and longitudinal changes in general cognitive ability in late life and to study whether the association is mediated through prevalence of CVD and dementia.

IV. To describe the association between BMI and dementia risk in older persons and to examine whether the risk is similar for men and women and for different age groups.

3. Methods

This thesis is grounded in three population-based studies, the Swedish Adoption/Twin Study of Aging (SATSA),[143] Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behaviour and Health among Elderly (Gender Study),[144] and the Finnish Lieto Study.[44] Table 1 summarizes the main characteristics of the studies.

3.1. The SATSA Study - Studies I and III

3.1.1. Participants and Procedure

The study sample was drawn from the STR,[145] and the registry was compiled from two cohorts. The older cohort consisted of twin pairs born before 1926. These participants were mailed questionnaires in 1963 that included questions about weight, height, smoking and alcohol habits, diseases, and so on. In 1973, a second cohort (born from 1926 through 1958) was mailed a questionnaire that included generally the same questions as had been asked of the older cohort. In 1986, a subsample of the STR was invited to participate in the SATSA study.[143] The origin of the project dates to 1978 when it was observed that an appreciable number of twins in the STR had been reared apart from one another. All twins who had been reared apart and a sample of reared-together pairs matched on birth year, county of birth, and sex were invited to participate in SATSA. These twins were sent a questionnaire in 1984. Among those twin pairs for whom both twins responded (N = 2072), a subsample of individuals, mainly over age 50, was invited to participate in an in-person testing (IPT) of health and cognitive functions. At the first IPT in 1986, 645 twins participated. Since then, these twins and all twins who turned 50 years of age since the last IPT were systemically interviewed and assessed on a battery of cognitive tests every three years (except in 1995) by trained research nurses in a primary care facility close to their homes.

Table. 1. Characteristics of the Studies Included in the Thesis

Study	Name of Study	N	Mean Age at Baseline (Range)	Design (N of IPTs) Years of Follow-up	Agreement and Associations in Focus	Covariates
I	SATSA*	774	64 (40–88)	Longitudinal (5) 21 years	Agreement between self-reported and assessed BMI†	Gender, dementia, BMI
II	Gender Study‡	498	74 (70–81)	Longitudinal (3) 8 years	Agreement between dementia diagnoses set at a consensus conference and medical records review, MMSE§, cognitive tests, nurse evaluations, and the Swedish IDR#	
III	SATSA	781	42 (25–63)	Longitudinal (5) 41 years	The association between BMI in midlife and general cognitive ability (composite score of 11 cognitive tests) in late life	Gender, age, education, smoking, alcohol, CVD**, diabetes, dementia
IV	Lieto Study	605	71 (65–92)	Prospective (2) 8 years	The association between BMI and dementia in late life	Gender, age, education, smoking, alcohol, CVD, diabetes

* Swedish Adoption/Twin Study of Aging, † Body Mass Index, ‡ Aging in Women and Men: A Longitudinal Study of Gender Differences in Health Behaviour and Health among Elderly, § Mini-Mental State Examination, # In-patient discharge registry, ** Cardiovascular diseases.

Specific for study I, among those 645 twins who participated in IPT1, 595 answered a corresponding questionnaire (Q2) in 1987 and filled out questions about height and weight. Questionnaires about health, psychological, and social factors were sent to the participants in the middle of the IPT data collections, which have taken about two years to complete. For the present study, five IPTs had matching questionnaire data: IPTs 1, 2, 3, 6, and 7. Data were collected between 1986 and 2007. Totally, data from 774 persons were available for analyses, because twins included in later IPTs also were included.

Specific for study III, among those who participated in the SATSA IPTs, the availability of BMI scores from midlife ranged from 61% to 89%, with higher availability for the first IPTs. In total, 781 individuals (60% women) had both a midlife BMI score reported in 1963 (56.5%) or 1973 (43.5%) mailed questionnaire and at least one completed neuropsychological assessment between 1986 and 2004.

3.1.2. Measurements

Height and weight were self-reported in 1963 and 1973 and in the questionnaire phases of SATSA. Weight and height were measured in clothing without shoes by a trained research nurse at the IPT.

Eleven cognitive tests are included in the SATSA cognitive test battery. Verbal abilities are tapped by WAIS information–short form,[146] Synonyms–form A,[147] and Analogies.[148] Figure Logic–form A,[147] Koh's Block Design,[149] and Card Rotation[150] assess spatial abilities. Memory tests include Digit Span (forward and backward),[146] Thurstone's Picture Memory,[151] and Names and Faces task.[152] Symbol Digit[153] and Figure Identification–form A[147] measure perceptual speed. Reliabilities for these tests range from 0.82 to 0.96.[1]

To create a measure of general cognitive ability, individual scores on the first principal component of all cognitive measures were obtained at IPT1.[1] To avoid adding any error to the latent growth curve model by using a principal component

that varied in definition at each time point, we standardized scores on each cognitive measure using the means and variance observed at IPT1, creating an identical metric for each cognitive measure at all five time points. Next, we created a global cognitive factor for each testing occasion by combining the now-standardized cognitive scores using the factor loadings from the principal-component analysis conducted at IPT1, thereby ensuring that the definition of the cognitive factor remained constant across testing occasions. Last, the factor scores were scaled into t-score metrics.[31,154]

Dementia was continuously screened for during the IPTs. Identification criteria included participants with low scores on the MMSE examination and/or cognitive tests, a history of dementia in their medical records, or suspicion of dementia by the research nurses; individuals who scored poorly on a telephone interview; and/or information from refuser protocols (that is, a proxy reported that the twin had cognitive problems).[2] All suspected cases of dementia were diagnosed during a consensus conference according to the DSM criteria used at the time of assessment.[37] All available information (research protocols, medical records, refuser protocols, and nurse notes) from the total study period was used.

Level of education was dichotomized as low (≤ 6 years) or high (> 6 years). Self-reported alcohol consumption, smoking, and CVD were evaluated in midlife using the 1967 or 1973 surveys, as well in the SATSA IPTs. Participants who reported that they never used alcohol during the entire study period were coded as non-drinkers; participants who reported that they had smoked at any time were coded as smokers. Self-reported data on heart attack, angina pectoris, thrombosis, heart insufficiency, diabetes, and stroke at least once during the study period were coded as presence or absence. Persons who reported use of antihypertensive medication and/or an assessed blood pressure above 140/90 mmHg twice or more during the IPTs were coded as hypertensive. The diseases were summed to form CVD scores, which ranged from zero to seven, with one point given if the disease or symptom was ever reported.

3.2. The Gender Study – Study II

3.2.1. Participants and Procedure

The Gender Study sample was drawn from the STR. Participants were unlike-sex twins born between 1916 and 1925, with both twins alive in 1995. The inclusion criteria have been described in detail previously.[144] The first IPT started in 1995 and comprised 249 twin pairs (N = 498). Experienced research nurses conducted the IPTs in the participants' homes. Each IPT involved an interview covering sociodemographic background data, administration of cognitive tests, health examination, drug registration, and blood sampling. Two subsequent IPTs were conducted, the second in 1999–2001 and the third in 2003–2005.

3.2.2. Measurements

At both the first and third IPTs, informed consent was sought to obtain medical records from hospitals and primary care facilities. The medical records were requested according to each participant's self-report, based on health care units they mentioned having contacted and which diseases they mentioned during the IPT. In cases in which it was revealed that the participant had been to additional units, usually during the medical record review, these records were also requested. Medical records were received for 99% of participants. Medical records reviews were performed independently by an experienced physician and the first author to ensure the reliability of the extraction of a dementia diagnosis. An explicit diagnosis of dementia in the record's diagnosis list and/or a physician's notification of dementia in the record text were coded as dementia. Physicians' recordings of cognitive dysfunctions such as memory disturbance were coded as cognitive impairments. It was sometimes seen that memory complaints from elderly persons were not confirmed by their physicians; these complaints were not coded as cognitive impairments. Inter-rater agreement was 99%, and in the few cases of disagreement, the two researchers discussed the cases and reached consensus.

The results of MMSE and six other cognitive tests were analyzed. Three tests from the Dureman & Sälde battery were applied:[147] the Synonyms test, which evaluates knowledge of verbal meaning; the Block Design test, which measures spatial reasoning with novel material; and the Identical Forms, which measures perceptual speed. Spatial ability was also assessed using the Card Rotation test.[150] Memory function was measured by both Thurstone's Picture Memory[151] and the 10-Word List for delayed free recall.[155]

The nurses evaluated the respondents on the Berger scale,[156] which measures social dependency hierarchically on a six-point scale. There were two further options for the research nurses to select: "normal functioning" and "impossible to judge, due to somatic or other problems." All participants in the present study were linked with the IDR by their unique personal identification numbers. The codes for dementia and senility from the International Statistical Classification of Disease and Related Health Problems (ICD)[157] Version 8 (290.00–290.19), Version 9 (290.A–290.X), and Version 10 (F00–F03, G30, F10.7, R54) were employed to identify persons with dementia.

In 2005, a subsample of 127 individuals was selected from the hospital and/or primary care medical records, all cases of diagnosis of dementia, notification about memory or cognitive disturbances, and/or a memory complaint. In addition, individuals who scored less than 24 out of 30 on the MMSE and/or less than 10 out of 40 on the Block Design test at any IPT were included, as were those who were determined by the research nurses to show signs of dementia. Each individual in the subsample was diagnosed at the consensus conference, which included one physician, two psychologists, and one specialized dementia nurse. Diagnoses were assigned following the DSM-IV.[37] The diagnosis of dementia was based on clinically relevant information, such as cognitive tests, medical records, biochemical blood values, and nurse evaluations (Berger scale). The amount of available data varied because some people had dropped out of the study or refused to participate in some tests, and/or the medical records were scarce.

3.3. The Lieto Study – Study IV

3.3.1. Participants and Procedure

This study was part of a prospective population-based study carried out in the municipality of Lieto, in southwestern Finland.[44] In 1990–1991, all residents of Lieto born in 1925 or earlier were invited to participate in the study (N = 1,283). Of these, 605 persons were still alive and had complete data from a second IPT in 1998–1999. In both IPTs, a trained nurse in a health care center interviewed participants about sociodemographic data, lifestyle factors (education, smoking, and alcohol use), and mental and physical health. Participants were asked to report all prescribed medications used during the previous seven days, and prescriptions and drug containers were checked. Medications were coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[158] Research physicians performed all physical examinations and clinical tests. In addition, the research physicians examined participant primary care medical records, including information from specialist visits and hospital care, and previous diagnoses were coded according to the ICD-10.[159]

3.3.2. Measurements

At baseline and at follow-up, a trained research nurse measured weight and height with participants in light clothing. The diagnosing of dementia in the Lieto study has been previously described in detail.[160] Briefly, all participants scoring below 24[47] on the MMSE, with a previously diagnosed dementia disorder or a note on cognitive impairments in medical records, and/or a suspicion of memory disorder or dementia during the interview and/or clinical examination were invited to a further clinical examination (n = 138). Caregivers or nursing staff were interviewed, and dementia was assessed according to the criteria of the DSM-IV.[37] All collected data were used in the diagnosis, such as laboratory tests, medical records, information from the caregiver/nursing staff, and MMSE scores. In cases of uncertainty or disagreement, a consensus was reached between the research physicians and a geriatrician on the research team.

Clinical diagnoses were made at the eight-year follow-up. Participants were defined as having diabetes mellitus if they had such a diagnosis (ICD-10 code E10–E14) in their medical records, were being treated with antidiabetic agents (ATC code A10), and/or had a fasting glucose level of 7.0 mmol/L or greater during the examination. Participants were coded as hypertensive if they had such a diagnosis (I10–I15) in their medical records, if they were entitled to reimbursements from the Finnish National Health Institute for hypertension medication, and/or if they had a systolic blood pressure of 160 mmHg or greater and/or diastolic blood pressure of 100 mmHg or greater at the examination. Twelve-lead resting electrocardiograms (ECG) were taken, and ECGs were coded using the Minnesota codes.[161] Thus, coronary heart disease was defined when at least one of the following criteria was present: (1) typical history of angina pectoris, (2) previous myocardial infarction, (3) ischemia on ECG: Minnesota codes 1.1–1.2 positive,[162] (4) history of coronary bypass surgery, or (5) history of coronary angioplasty.[163] Atrial fibrillation was coded as present in participants with a diagnosis in the medical record (I48) and/or atrial fibrillation on the ECG. If the participant had a diagnosis of stroke (I60–I64, I69) in the medical records, and/or had a subjective history of stroke with neurological symptoms persisting for more then 24 hours, as verified in the clinical examination, he or she was coded as suffering from stroke. Data on hypertension, coronary heart disease, atrial fibrillation, and stroke were coded as present or absent and summed to form a CVD score (range 0–4). Smoking was also assessed in the first phase, and the participants were coded as either ex-smokers/current smokers or nonsmokers. Alcohol use was assessed in the second phase, and the participants were coded as abstainers or non-abstainers.

All participants who had died before the second investigation phase were linked with the official Finnish Cause of Death Registry[164] by their unique personal identification number. The codes for dementia from ICD-9 and 10 were employed to identify persons with dementia.

3.4. Statistical Analyses

3.4.1. Over All Studies

Differences among groups were assessed with χ^2-tests or *t*-tests when appropriate, calculated with SAS version 9.1[165] or with the latest version of SPSS[166] at the time of analysis. Correlations between self-reported and measured height, weight, and BMI were calculated using Pearson's correlation coefficient. Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) were calculated according to Altman.[167] BMI was calculated as weight in kilograms divided by height in meters squared. In the primary analyses, BMI was used as a continuous variable, while for descriptive purposes, persons were classified as underweight when the BMI score was below 18.5, normal weight at BMI 18.5–24.9, overweight at BMI 25–29.9, and obese when the BMI scores were 30 and over, according to the WHO standard.[15]

Latent Growth Curve Models

In studies I and III, we employed latent growth curve modeling to measure change over time. Latent growth curve models measure and allow for comparisons of individual trajectories of decline as well as an average trajectory of decline across the entire sample. Individual changes are assumed to follow the mean path of change for the total population, but the random effects allow the individual levels of function to be higher or lower and the rate of decline or growth to be faster or slower. A phenotypic latent growth model with a full maximum-likelihood estimate technique was used in the growth models.[168,169] Both linear and quadratic models were considered. Because we could not assume that the twins were independent of each other, models were adjusted to account for the correlation within twin pairs. PROC MIXED[165] in SAS was used to fit the latent growth curve models.

3.4.2. Specific Study I

Regardless of when a person entered SATSA, the first measurement occasion was coded as measurement occasion 1. Bland-Altman plots were also used to illustrate and examine agreement between measured and self-reported values.[170] The

difference between measured and self-reported BMI values was plotted against the mean of the two BMI values. Limits of agreement were calculated as the mean difference plus two standard deviations.

3.4.3. Specific Study II

For all comparative calculations, the consensus diagnosis was used as the gold standard. For statistical analyses, two levels of medical records were calculated. Level one (Medical Records I) included only those individuals with an explicit diagnosis of dementia. Level two (Medical Records II) included both individuals with an explicit dementia diagnosis and those with some kind of recording of cognitive disturbance verified by a clinician.

Because cognitive test scores often are used as a proxy of dementia, the last available cognitive test results for each individual were dichotomized at the 10th percentile, which has been proposed to be a fair proxy of dementia.[48,171] MMSE was dichotomized at 24, 10-Word List delayed free recall at 4, Thurstone's Picture Memory at 15, Identical Forms at 7, Card Rotation at 17, Block Design at 9, and Synonyms at 10. Likewise, difference scores were calculated between the first and second IPTs and between the second and third IPTs and dichotomized at the 10th percentile. A decrease in the MMSE > 4, 10-Word List delayed free recall > 2, Thurstone's Picture Memory > 5, Identical Forms > 4, Card Rotation > 13, Block Design > 6, and Synonyms > 3 during a four-year period were assumed to indicate the development of dementia.

The current diagnostic criteria for various types of dementia emphasize the multifactorial nature of cognition; hence, we created two variables to include this feature. To be considered as having possible dementia in the first variable (cognitive battery[1]), the participant needed to have an impairment in at least two cognitive domains, as indicated by a cognitive test score below the 10th percentile, one of which was memory (Thurstone's Picture Memory and/or 10-Word List delayed free recall). Those with fewer than five available measures were excluded from analysis.

The second criterion (cognitive battery[2]) was calculated in the same way, with the exception that the MMSE was included and those with fewer than six available measures were excluded from analysis. The final nurse evaluation on the Berger Scale was used. Those respondents who were coded by the research nurses as impossible to evaluate were coded as missing.

3.4.4. Specific Study III

Growth curves were fit to establish linear and nonlinear age trends for general cognitive ability at the mean-centered age of 65, the age at which cognitive abilities are considered to begin to decline.[31] BMI was centered at 25, the value considered to be the breaking-point between normal weight and overweight.[15] A stepwise procedure was adopted to evaluate longitudinal trajectories. Interaction terms between linear and quadratic age, sex, and BMI scores were added to the model. We used -2log likelihood test to evaluate the multi-parameter hypothesis testing, starting with the full model that included all interaction terms and covariates, followed by stepwise exclusion of interaction terms. At each step, we controlled for age, educational level, alcohol use, smoking, and CVDs. Moreover, cohort was controlled for because the members of the younger cohort had a shorter follow-up time from baseline. Because SATSA data included individuals with dementia, all analyses were carried out twice: once including all persons with dementia and once excluding them.

3.4.5. Specific Study IV

Hazard ratios (HR) for dementia were calculated using Cox regression analyses to account for the follow-up time. In the first step, the analyses were adjusted for age, sex, and education level (model 1); then, diabetes and CVD scores were added (model 2); and in the last step, smoking and alcohol use were also controlled for (model 3). The risk of dementia was first analyzed for the total sample, then separately for men and women, and finally for younger (65–70 years) and older participants (71 years and above).

3.5. Ethical Considerations

Studies of the aging process and elderly from various perspectives are important for understanding the specific characteristics of aging and the needs of an age group that is continuously growing all over the world. Longitudinal research is especially suitable to understanding the aging process because it can separate changes due to aging from cohort effects, selection bias, etc. None of the data for the studies were collected for the specific aims in this thesis; thus, none of the participants were aware of the specific aims of the present thesis, but the participants have been aware that the data will be used for aging research. It is my personal belief that it would be more unethical not to use the already collected data than to use it, because many people have devoted their time to acquiring it and a lot of money has been spent on the process.

The fundamental principle of the Declaration of Helsinki is respect for the individual and the right to give informed consent regarding participation in research, both initially and during the course of the research. All participants were sent a personal letter explaining the purpose of the study at each IPT, the content, and the time of duration. It is also emphasized that the involvement is voluntary and withdrawal can be done at any time point without any need for an explanation. Thereafter, the research nurses contacted the participants by phone, explaining the procedure in depth and giving participants the opportunity to ask questions. At the IPT, participants were asked for informed consent and permission to request the medical records. Research protocols and data sets are handled with confidentiality, and the results are presented so that no single individual can be identified.

Specific ethical considerations in the present studies are whether the participants may be harmed by the extensive physical and psychological evaluations. In general, the participants expressed that they liked the opportunity to share their experiences and to have an extra free medical examination. All interviews were performed by research nurses with long work experience (often from elderly care) and judged by the principal investigators as being able to handle emotional reactions. If the

participant expressed or was judged by the research nurses to be unable to perform some tests because of tiredness or other limitations like cognitive impairments, the session was shortened or terminated. In SATSA and the Gender Study, all participants were offered something to eat and drink during a break in the middle of the research sessions to give them some rest and renewed energy. In the Lieto study, this break was not needed because the research sessions were shorter.

SATSA and the Gender Study were approved by the Ethics Committee at the Karolinska Institute, Stockholm, Sweden, Dnr 80:80, 84:61, 86:148, 93:226, and 98:319, respectively, and approved by the Swedish Data Inspection Authority. The Lieto study was approved by the Joint Commission of Ethics for the Hospital District of Southwest Finland.

4. Results

4.1. Study I - Agreement between Self-reported and Measured Height, Weight, and Body Mass Index in Late Life

4.1.1. Study Sample Characteristics

At the first measurement occasion, the mean age was 63.9 years (range 40–88), and the mean BMI was 25.6 (range 16.3–46.1). Less than one percent (0.9%) of the sample had a BMI below 18.5, 47.4% had a BMI between 18.5 and 24.9, 40.1% had a BMI between 25–29.9, and 11.6% had a BMI above 30. Approximately 60% of participants were women, and the gender distribution was fairly constant over all measurement occasions. During the first four measurement occasions, 72 persons were diagnosed with dementia. Table 2 shows the agreement measures between self-reported and assessed height, weight, and BMI at each measurement occasion. The correlations at each measurement occasion were substantial and significant (P < .001). The kappa coefficients of BMI dichotomized at 25 indicated substantial agreement over all measurement occasions, but this agreement declined over time. The sensitivity values were also high but declined over time. The specificity values were high over all measurement occasions and did not decline over time.

Table 2. Pearson's Correlation Coefficients between Self-reported and Measured Height, Weight, and Body Mass Index (BMI), and the Kappa Coefficients, Sensitivity, and Specificity for BMI, Dichotomized at 25 kg/m²

Measurement Occasion	N	Height	Weight	BMI	BMI		
		r	r	r	Kappa	Sensitivity	Specificity
1	774	0.98	0.97	0.94	0.81	0.86	0.95
2	615	0.97	0.98	0.95	0.78	0.84	0.94
3	491	0.98	0.98	0.95	0.79	0.79	0.98
4	273	0.97	0.97	0.93	0.74	0.74	0.96
5	156	0.97	0.97	0.93	0.72	0.72	1.00

4.1.2. Changes over Time

Table 3 shows the mean values and mean differences between self-reported and measured height, weight, and BMI for each of the measurement occasions. Height was overestimated by 0.9 to 1.2 cm, weight was underestimated by 0.5 to 1.7 kg, and BMI was underestimated by 0.5 to 1 kg/m^2. Latent growth curve modeling revealed that the difference between self-reported and assessed BMI and height increased significantly with age ($P < .001$). For each year, the difference between self-reported and measured BMI and height increased by 0.02 kg/m^2 and 0.4 mm, respectively. This trends means that over 20 years, there is an increase in misclassification bias of 0.4 kg/m^2 for BMI and 8 mm for height. We found no statistically significant linear increase in self-report bias for weight.

4.1.3. Gender Differences

Because previous studies have reported gender differences, sex was also included in the model. Compared to men, women significantly underreported their BMI by 0.3 kg/m^2 ($P < .001$) and their weight by 0.4 kg ($P < .05$). They also tended to overestimate their height more than men, by 0.3 cm ($P = .08$). However, there was no significant difference in the slope between men and women; i.e., the difference between men and women regarding misclassification of height, weight, and BMI remained stable over time.

4.1.4. Reliability of Self-reported Body Mass Index Related to Dementia, Actual Body Mass Index, and Time Point of Self-report

Dementia status did not significantly affect the reliability of self-reported BMI. Additionally, results did not change substantially when persons diagnosed with dementia during the study period were excluded from the analysis. To measure potential under- and overestimation as a function of BMI, measured BMI at IPT1 was included in the latent growth curve models. For each unit increase in BMI at baseline, the underreporting of weight increased by 0.2 kg ($P < .001$), and overestimation of height increased by 0.5 mm ($P < .05$). The underestimation of

Table 3. Means (standard deviations (SD)) and Mean Differences (SD) for Self-reported and Measured Height, Weight, and Body Mass Index (BMI)

Time	Height			Weight			BMI		
	Reported	Measured	Difference	Reported	Measured	Difference	Reported	Measured	Difference
1	167.3 (9.3)	166.4 (9.7)	0.9 (2.1)	70.1 (12.8)	71.2 (13.4)	-1.0 (3.2)	25.0 (3.5)	25.6 (3.9)	-0.6 (1.3)
2	167.2 (9.7)	166.2 (9.9)	1.0 (2.3)	71.1 (13.7)	71.6 (14.0)	-0.5 (2.7)	25.3 (3.8)	25.8 (4.0)	-0.5 (1.2)
3	166.6 (9.9)	165.6 (10.2)	1.1 (2.1)	71.0 (13.7)	72.2 (14.3)	-1.2 (2.9)	25.5 (3.8)	26.2 (4.2)	-0.8 (1.2)
4	166.2 (9.7)	165.0 (9.6)	1.2 (2.3)	71.2 (13.3)	72.4 (13.8)	-1.2 (3.4)	25.7 (3.9)	26.5 (4.1)	-0.8 (1.5)
5	164.8 (9.9)	163.6 (9.8)	1.2 (2.5)	69.0 (11.8)	70.7 (12.4)	-1.7 (3.1)	25.3 (3.4)	26.4 (3.7)	-1.0 (1.3)

BMI consequently increased by 0.1 kg/m^2 (P < .001). This outcome is also illustrated by the Bland-Altman plots in Figure 2. Visually, it also appears that older persons with higher BMI scores do not underestimate their BMI to the extent they did when they were younger.

The reliability of self-reported BMI in regards to the measurement of height and weight before or after self-report was evaluated at IPT1. In total, 95 persons attended IPT1 three months or less before the questionnaire phase, and 84 persons attended three months or less following completion of the questionnaire. Persons who were assessed after the self-report tended to underestimate their weight by about 0.7 kg (P = .10) and BMI by 0.3 kg/m² (P = .11) more than persons who first had their height and weight measured and then self-reported. There was no significant difference between the groups for accuracy of height.

4.1.5. Analyses of Outliers

For height, weight, and BMI, persons above two standard deviations (SD) were compared with persons within two SD both quantitatively and qualitatively to identify factors leading to under- and overestimation. There was no significant difference in prevalence of dementia between the outliers and persons within the normal range, as tested with Fisher's exact test. Some of the outliers had actually changed their weight dramatically between two measurement occasions, and when the questionnaire arrived between these measurement occasions, it led to increased over- or underestimation of their weight. Some of the outliers seem to be due to transpositions, i.e., a person self-reporting his height as 169 cm several times, but writing 196 cm on one occasion.

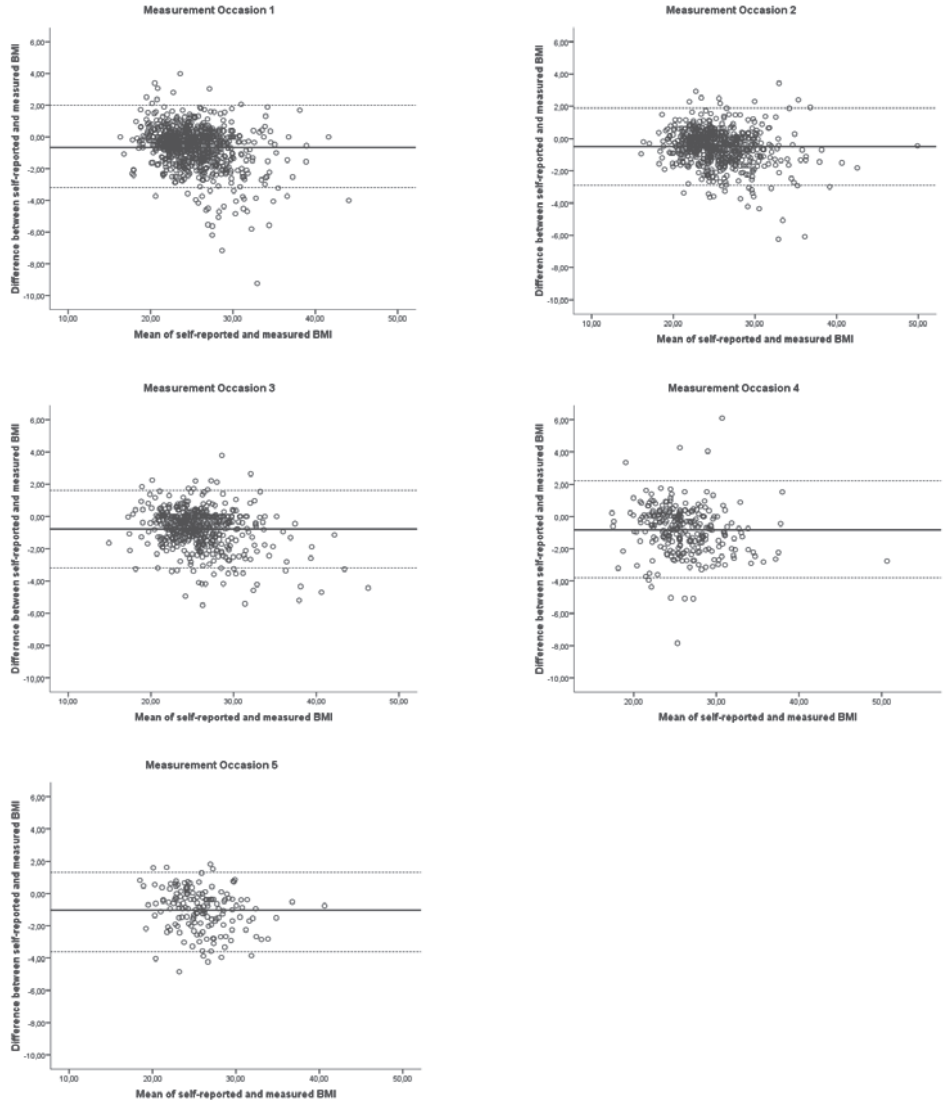

Figure 2. Bland-Altman Plots of Difference between Self-reported and Measured Body Mass Index (BMI) versus Mean of Self-reported and Measured BMI at Each Measurement Occasion.

4.2. Study II - Usefulness of Various Data Sources to Identify Persons with Dementia

4.2.1. Study Sample Characteristics

The average age in this study was 74.5 years (range 70–81) at baseline, and Table 4 shows the sample characteristics. The consensus conference identified 87 individuals (17% of the total sample) with dementia. There were no significant differences in age or education between persons considered to have dementia and those considered not to have it.

4.2.2. Medical Records

Table 5 shows the sensitivity, specificity, PPV, NPV, and kappa coefficient for the medical records. Fifty-six persons had dementia explicitly documented in their medical records, and twenty-three persons had recordings of cognitive dysfunction. Accordingly, when notes about cognitive dysfunction were included, medical records review yielded higher agreement measures. Of the 411 persons who were not diagnosed with dementia, five were given a dementia diagnosis in the medical records but not at the consensus conference. Two were evaluated as cognitively impaired but not demented, and one had questionable dementia according to the consensus conference. One had several severe physical diseases. The fifth person participated in the first two investigations and had a questionable notification of dementia in the medical records after the last in-person test. There was no age difference between those identified as having dementia in the medical records and those who were not identified.

Table 4. Sample Characteristics of Persons Diagnosed with Dementia and Persons Not Diagnosed with Dementia

	Dementia	Not Diagnosed with Dementia
	n (%)	n (%)
Gender		
Men	45 (51.7)	204 (49.6)
Women	42 (48.3)	207 (50.3)
Education		
≤ 6 years	54 (62.8)	228 (55.5)
> 6 years	32 (37.2)	183 (44.5)

Table 5. Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Kappa Coefficient (kappa) for Medical Records, Cognitive Tests, Nurse Evaluations, and Swedish In-patient Discharge Registry (IDR), N = 491

	Sensitivity	Specificity	PPV	NPV	Kappa
Medical Records I*	0.57	0.99	0.89	0.91	0.65
Medical Records II†	0.83	0.98	0.91	0.96	0.84
MMSE	0.72	0.90	0.61	0.94	0.58
10-Word List, free recall	0.55	0.82	0.36	0.91	0.31
Thurstone	0.46	0.90	0.46	0.90	0.36
Identical Forms	0.38	0.88	0.39	0.88	0.27
Card Rotation	0.25	0.92	0.35	0.88	0.19
Block Design	0.55	0.85	0.42	0.90	0.36
Synonyms	0.27	0.94	0.38	0.87	0.21
Cognitive battery‡	0.55	0.87	0.42	0.92	0.37
Cognitive battery§	0.73	0.85	0.46	0.95	0.47
Nurse evaluations	0.80	0.96	0.81	0.96	0.77
Swedish IDR	0.26	0.97	0.66	0.86	0.31

* Including only explicit dementia diagnoses, † Including both explicit dementia diagnoses and notes of cognitive disturbances, ‡ Excluding MMSE, § Including MMSE.

4.2.3. Cognitive Tests

Table 5 lists the sensitivity, specificity, PPV, NPV and kappa coefficient for each cognitive test. MMSE scores at the 10th percentile rated highest among the cognitive tests in all agreement measures. The cognitive battery[2] (including the MMSE score) yielded approximately the same numbers, although with lower kappa coefficient and PPV and higher sensitivity. There were no main differences between the other cognitive tests. Sensitivity, specificity, PPV, NPV and kappa coefficient were also calculated at the 5th percentile. As expected, for all tests, sensitivity decreased whereas specificity increased at the 5th percentile, and PPV increased and NPV decreased.

4.2.4. Nurse Evaluations

As Table 5 shows, research nurse evaluations on the Berger scale yielded high agreement measures. The missing values (n = 28) refer to those who could not be evaluated on the last measure occasion because of somatic or other problems. Nine of these had dementia according to the consensus conference.

4.2.5. In-patient Discharge Registry

The dementia identification in the Swedish IDR had low sensitivity, although specificity was high. Thirty-five individuals were identified as having dementia by the IDR, and 23 of these were diagnosed with dementia by the consensus conference. Of those not identified as having dementia by the consensus conference, eight did not reach the criteria for inclusion. Of these, three were evaluated three times during the IPTs without any indication of dementia. The other five participated only in the first IPT; they had a dementia diagnosis in the IDR after our last contact with them. The remaining four persons were evaluated by the consensus conference. Two were evaluated as cognitively impaired but not demented; another person participated in two investigations and was diagnosed with dementia according to the IDR after our last contact. The fourth person participated in all three IPTs without any indication of dementia. There were no

age differences between those identified as having dementia by the IDR and those not identified.

4.3. Study III - Midlife Overweight and General Cognitive Ability in Late Life

4.3.1. Study Sample Characteristics

The mean age at midlife was 41.6 years (range 25–63). Table 6 presents the participant characteristics according to sex. At midlife, the mean BMI was 23.7 (range 17.1–38.5), 2% of the sample were underweight, 68.4% were normal weight, 25.9% were overweight, and 3.7% were obese. The composite score of general cognitive ability ranged from 22.81 to 75.73 during the study period, with higher scores indicating better cognitive performance. In general, men had a non-significantly higher level of cognitive functioning than women. There was no significant difference in midlife BMI between the 68 participants who developed dementia and those who were cognitively intact at death or in 2005.

Table 6. Sample Characteristics by Sex (N = 781)

	Men	Women	*P* value
	n = 307	n = 474	
Age 1986, mean (SD)*	59.6 (10.2)	61.6 (11.2)	.007
Midlife BMI†, mean (SD)	24.2 (2.6)	23.3 (3.3)	.000
CVDs‡, mean (SD)	2.0 (0.1)	1.9 (0.1)	.288
Low education (≤ 6 years) (%)	131 (47.1)	147 (52.9)	.281
Alcohol abstainers (%)	23 (7.1)	113 (23.3)	.000
Present/ex-smoker (%)	245 (75.9)	207 (42.6)	.000
Cognitive ability§ IPT¶1 (n = 574), mean (SD)	50.9 (10.7)	49.4 (9.7)	.085

* Standard Deviation, † Body Mass Index, ‡ Cardiovascular diseases, including self-reported heart attack, angina pectoris, heart insufficiency, high blood pressure, thrombosis, stroke, and diabetes during the study period, § First principal component, ¶ In-person testing.

4.3.2. Midlife Body Mass Index and Cognitive Ability

Significant average performance effects (intercept) on general cognitive ability were found for BMI in midlife when educational level, cohort, alcohol use, smoking, and CVDs were controlled for (Table 7). Persons with a higher BMI in midlife had lower general cognitive ability in late life. Moreover, their cognitive ability declined faster, as indicated by the interaction term between age and BMI (Table 7). Figure 3 illustrates the trajectory of change in global cognitive function from mid to late life by BMI (21 and 25). There were no significant interaction terms between BMI, sex, linear age, and quadratic age, and adding these interaction terms did not significantly improve the model, as evaluated by the -2log likelihood test. Women had a non-significant lower general cognitive ability than men (P = .085). However, there were no significant interaction terms between sex and linear age, quadratic age, or with BMI, demonstrating that there were no sex differences in the intercept or the slope, as Figure 3 shows. When persons diagnosed with dementia during the study period were excluded from the analysis, the association between midlife BMI and cognitive function became somewhat stronger (Table 7), but the trajectory did not change.

Table 7. Relationship between Midlife Body Mass Index (BMI) and Changes in General Cognitive Ability, Controlling for Cohort, Education, Cardiovascular Diseases, Smoking, and Alcohol Use

	All		Excluding Persons with Dementia	
Model term	Estimate (SE)	*P* value	Estimate (SE)	*P* value
Age*	-0.288 (0.020)	< .0001	-0.285 (0.020)	< .0001
Age²†	-0.011 (0.001)	< .0001	-0.010 (0.001)	< .0001
BMI‡	-0.348 (0.112)	.002	-0.434 (0.118)	.0002
Age*BMI§	-0.015 (0.006)	.011	-0.015 (0.006)	.012

* Linear longitudinal change defined by age, † Curvilinear longitudinal change defined by age, ‡ Intercept, difference in mean BMI scores, § Slope, difference in trajectory of change due to age and BMI scores.

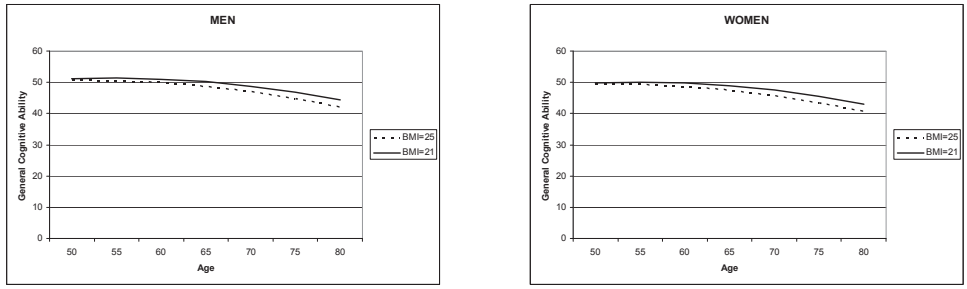

Figure 3. Longitudinal Association between Midlife Body Mass Index (BMI) Scores and General Cognitive Ability Measured by the First Principal Component, Including Persons with Dementia.

4.4. Study IV – Body Mass Index in Old Age and Dementia Risk

4.4.1. Study Sample Characteristics

At baseline, the mean age was 70.8 (SD = 5.5) and the average BMI was 28.1 (SD = 4.4) (Table 1). Those who had died before the second study phase had lower BMI scores (26.8, SD = 5.4) at baseline. Of those 419 persons who had died before the second phase, 55 (13.1%) had been diagnosed with dementia according to the Finnish Cause of Death Registry. Because only four persons were underweight (BMI less than 18.5) at baseline, they were included in the normal weight group. None of the underweight persons were diagnosed with dementia during the follow-up. During the eight-year follow-up, 86 people developed dementia. Those who developed dementia had lower BMI scores at baseline ($P < .05$). Their BMI scores also declined more during the eight-year follow-up ($P < .001$) (Table 8). Persons with dementia were also older ($P < .05$) and less likely to have reported using alcohol ($P < .05$). The median BMI score was 27.5 for men and 27.9 for women, and the median ages were 69 and 70, respectively. There were statistically significant differences in the BMI scores of men and women ($P < .05$) and for their scores for age ($P < .05$), smoking ($P < .05$), and alcohol behavior ($P < .05$) (Table 9). Women had higher BMI scores, were older, had a higher prevalence of CVDs, and had never smoked or used alcohol. More women (n = 59) than men (n = 27)

were diagnosed with dementia, but the difference did not reach significance (P = .10).

4.4.2. Association between Body Mass Index and Dementia Risk

The Cox regression analyses were performed in three steps, but because the hazard ratios did not differ substantially among the models, only the fully adjusted model is presented in Table 10. The analyses, controlling for age, gender, education, diabetes, CVD, smoking, and alcohol use, showed an association between BMI scores at baseline with dementia eight years later (HR = 0.92; 95% confidence interval (CI) = 0.87–0.97). Persons with a one-unit increase in BMI scores had an 8% lower dementia risk. Because it is possible that mild preclinical dementia could account for our findings, we repeated the analysis, excluding persons who had a dementia diagnosis made in their medical records within the first four years after the baseline (N = 30). The association did not substantially change (HR = 0.93; CI = 0.86–0.99). Neither did the result change substantially when we excluded persons with a BMI score below the 10th percentile (BMI < 22.9) (HR = 0.92; CI = 0.85–0.99).

The total sample was divided into three groups according to the standard BMI categorization: normal weight (including those four persons with BMI scores below 18.5), overweight, and obese. Figure 4 shows the results of the Kaplan-Meier estimate of survival functions over eight years. Participants with a BMI below 25 had a higher incidence of dementia compared with those with a BMI score of 25 and above. The separate analyses of men and women indicated a significant risk of dementia for women with lower BMI scores (HR = 0.90; 95% CI = 0.84–0.96), but not for men (HR = 0.95; 95% CI = 0.84–1.07). The sample was also divided into two age groups based on the mean age. In the older age group, 63 persons were diagnosed with dementia and 21 in the younger group. The association was significant in the older age group (71–92 years of age at baseline) (HR = 0.92; 95% CI = 0.86–0.98), but in the younger age group (65–70 years of age at baseline), the association did not reach significance (HR = 0.92; 95% CI = 0.82–1.03).

Table 8. Characteristics of the Sample Population According to Dementia Status

Characteristics	All (N = 605)	No Dementia (n = 519)	Dementia (n = 86)
Mean age ± SD[†] (years)	70.8 ± 5.5	70.0 ± 4.9	75.6 ± 6.5*
BMI[‡] at baseline ± SD	28.1 ± 4.4	28.3 ± 4.4	26.8 ± 4.3*
BMI at follow-up ± SD	26.5 ± 4.8	26.9 ± 4.6	23.7 ± 5.1*
BMI < 25 (%)	23.1	20.8	37.2
BMI 25–29.9 (%)	49.1	50.1	43.0
BMI ≥ 30 (%)	27.8	29.1	19.8
Education (% ≤ 6 years)	70.2	69.9	72.1
Gender (% women)	60.5	68.6	59.2
CVD[§] ± SD	1.13 ± 0.83	1.10 ± 0.81	1.28 ± 0.97
Diabetes (%)	16.5	16.0	19.8
Nonsmokers (%)	66.5	65.9	69.8
Alcohol abstainers (%)	56.2	52.5	79.5*

* Significant at the 0.05 level, [†] Standard Deviation, [‡] Body Mass Index, [§] Cardiovascular diseases including coronary heart disease, hypertension, atrial fibrillation, and stroke.

Table 9. Characteristics of the Sample Population According to Sex

Variables	Men (n = 239)	Women (n = 366)
Mean age ± SD[†] (years)	70.1 ± 5.3	71.3 ± 5.6*
Dementia (% yes)	11.3	16.2
BMI[‡] ± SD	27.6± 4.0	28.4 ± 4.6*
BMI < 25 (%)	23.8	22.7
BMI 25–29.9 (%)	56.1	44.5
BMI ≥ 30 (%)	20.1	32.8
Education (% ≤ 6 years)	66.5	72.7
CVD[§] ± SD	1.18 ± 0.78	1.25 ± 0.76
Diabetes (%)	17.2	16.1
Nonsmokers (%)	31.2	89.3*
Alcohol abstainers (%)	40.8	66.2*

* Significant at the 0.05 level, [†] Standard Deviation, [‡] Body Mass Index, [§] Cardiovascular diseases including coronary heart disease, hypertension, atrial fibrillation, and stroke.

Table 10. Cox Proportional Hazards Model of Continuous Body Mass Index Scores and Risk of Dementia, Adjusted for Age, Gender, Education, CVD*, Diabetes, Smoking, and Alcohol Use

Participants	HR[†], 95% CI[‡]
All	0.92 (0.87–0.97)
Men	0.95 (0.84–1.07)
Women	0.90 (0.84–0.96)
Younger group (65–70 years)	0.92 (0.82–1.03)
Older group (71 years and over)	0.92 (0.86–0.98)

* Cardiovascular diseases including coronary heart disease, hypertension, atrial fibrillation, and stroke, [†] Hazard ratio, [‡] Confidence interval.

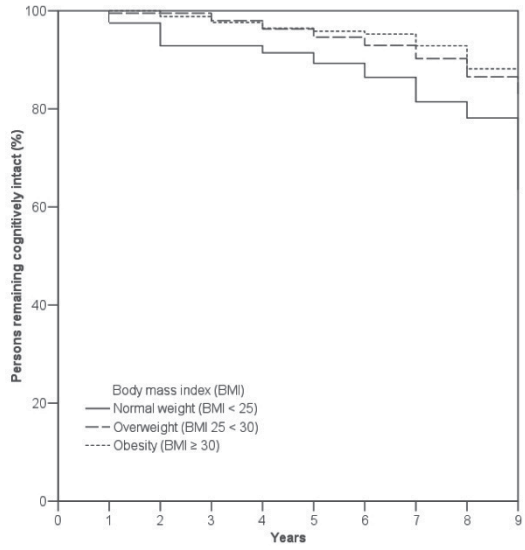

Figure 4. Body mass index and risk of incident dementia, controlling for age and sex.

Because a U-shaped association between BMI scores and risk of dementia has been reported, we categorized BMI scores into five groups at the 20th percentiles, using the middle percentile as a reference group. There was a significant association only between the lowest percentile and dementia (HR = 2.1; 95% CI = 1.07–4.2), indicating an increased risk of dementia among persons with low BMI scores.

5. Discussion

This dissertation presents several new and unique findings. The accuracy of self-reported BMI does not change substantially over time in old age. The review of medical records, nurse evaluations, and MMSE scores yielded the highest agreement with dementia diagnoses from a consensus conference. High BMI scores in midlife are related to lower cognitive ability and steeper decline in late life, independently from dementia and comorbid CVDs. On the other hand, high BMI scores in late life are associated with less dementia risk. This chapter discusses these findings in detail.

5.1. Self-reported Body Mass Index

It has been suggested in cross-sectional studies that the reliability of height is less valid in old age compared with young age.[18,22,23,26] Our longitudinal study supports this notion but indicates that the increase in misclassification bias is very small. Participants overestimate their height by a mean of approximately 1 cm; for each year, this misclassification bias increases by 0.4 mm. Over 20 years, the increase in misclassification bias is less than 1 cm. Underestimation of height in old age is likely to be the result of individuals reporting their height as measured in early adulthood and/or being unaware of changes in stature. More women than men overestimated their height in SATSA. This finding is similar to results from several other studies,[18,26] although some authors report no difference between genders[22] or that men overestimated more.[172] Because of their higher risk of osteoporosis, women are more prone to decreases in height than men,[173] and the prevalence of osteoporosis has been associated with an increased overestimation of height in old age.[25] On average, participants underestimated their weight by 0.5 to 1.5 kg, and women were more likely than men to underreport their weight. Several cross-sectional studies[22,23,26,27] indicate that the reliability of self-reported weight increases with age. Even though our results do not support that notion, our data do show

that the misclassification bias for weight among both men and women does not increase over time.

Longitudinal analyses revealed that the difference between self-reported and assessed BMI increased with advancing age, in agreement with results from cross-sectional studies.[18,23,26] In contrast with these studies, we found that the increase in misclassification bias is small, approximately 0.02 kg/m^2 a year. Over 20 years, this slight increase results in an increase of BMI misclassification bias of 0.4 kg/m^2, less than the misclassification bias at any single measurement occasion. Misclassification bias in BMI is mainly attributed to a lack of awareness about changes in height and not in weight. Even though there is a high correlation between self-reported and measured BMI over time and a small mean difference between self-reported and assessed BMI, when BMI was used as a dichotomized variable, the prevalence of overweight was underestimated, as in other studies.[18,21,23,25,26,174]

Also in agreement with previous reports,[17,20,22,23,26] persons with higher BMI scores underestimated their actual BMI to a greater extent than thinner persons. It is likely that social pressure to be slim also exists in old age. However, a higher discrepancy between self-reported and assessed BMI among persons with higher BMI seemed to attenuate a bit with increasing age (see Figure 2), a finding that also has emerged in two previous cross-sectional studies.[22,23] It might be speculated that there is less social pressure to be thin among very elderly persons.

In the present sample, there were some extreme outliers, as can be seen in the Bland-Altman plots. Hypothetically, this outcome could be attributed to a greater degree of dementia among the individuals that these outliers represent. However, dementia did not affected the accuracy of self-reported BMI in this study or in the Canadian Study of Health and Aging.[20] This lack of effect might arise from the small numbers of persons with dementia in the present study or because persons in the early stages of dementia might still remember their height and weight, while

those with severe dementia had dropped out of the study. Persons diagnosed with dementia might also report their weight as they recall it from earlier in life. Because the normal trajectory of weight is towards weight gain over the life span and weight loss in old age,[175] a finding particularly true for persons with dementia, they might by chance report their actually weight. Some of the persons represented by the outliers had actually changed their weight dramatically between the assessment and self-report, as indicated by later assessments. Other outliers were the result of errors, such as transposing numbers.

Strengths and Limitations

The main strength of the present study is its longitudinal and population-based design; the accuracy of self-reported height, weight, and BMI previously only have been evaluated cross-sectionally, which includes methodological limitations like selection bias and cohort differences. However, the longitudinal design might also skew results; individuals who had recently seen a health professional might provide more accurate information about body measures.[27] The participants in SATSA have had their weight and height measured every three years, and if they requested information about their height and weight, which all did with only a few exceptions, the research nurses provided them with the information. A three-year time span might hardly be considered recent. Although another study showed that recent measurements of height and weight did not really improve the reliability of self-reported values,[172] people in the present study who had undergone weight and height measurements three months before the self-report tended to underestimated their weight and BMI less than persons assessed after the self-report. On the other hand, we might underreport the reliability of weight. In SATSA, the participants' weight was assessed in clothes, but we believe that most people report their morning weight without clothes. Adding about 1 kg to the self-reported weight would remove most of the difference between self-reported and measured weight. As already discussed, some people also changed their weight substantially during the time lag between the self-report and assessment, which contributed to an underestimation of the accuracy of self-reported weight and BMI. Given these

potential sources of error, the mean differences in estimated and measured weight and BMI are quite small.

5.2. Identification of Dementia – Usefulness of Various Data Sources

The validity and reliability of the variables are of critical importance in all studies. This study shows that the reliability of medical records and nurse evaluations is high, while many dementia cases are not captured with retrieval from the Swedish IDR.

About half of the persons whom the consensus conference considered to have a dementia diagnosis had an explicit dementia diagnosis in their medical record. But, in four out of five dementia cases, the physicians were aware of memory problems and/or had made a dementia diagnosis. These results are similar to those from the Lieto study,[44] the Women's Memory Study,[43] and in a study from Oregon in the U.S.[45] All three studies reported identification rates between 70–80% with medical records review in the more severe dementia cases. However, they also reported that the identification rate was lower in mild dementia. In a study of a primary care center in Linköping, Sweden, which included a sample of patients age 70 years and over,[42] and in a cohort study of a health care practice in the United States, including patients age 60 years and over,[41] only one out of four primary care patients with moderate to severe dementia had documented diagnoses in their medical records The most probable explanation of these differences is the time factor: The three earlier mentioned studies with higher detection rates were collected more recently. A German longitudinal study of general practitioners' knowledge of dementia[176] found that physicians' knowledge about diagnosing dementia has increased over the last 10 years. This increase may arise from increasing awareness of dementia because of progress in modern therapy for AD, and increasing attention in both research and the news media. The lack of explicit dementia diagnoses and clinical work-up,[41,44,45] even when physicians were aware of memory problems, can be attributed to

factors like a lack of knowledge and education,[177-179] insufficient time,[179] and difficulty disclosing a diagnosis of dementia to the patient.[177,179]

The present results show that the MMSE is a fair predictor of dementia, which is similar to results from other studies.[48,49,180] We also showed that the MMSE was a better proxy of dementia than a cognitive test battery. This result conflicts with some findings of the MoVIE survey, which showed the opposite result,[48] whereas another outcome from the same study showed that the MMSE and a cognitive test battery yielded about the same sensitivity and specificity values.[49] If cognitive test results are only quantitatively evaluated, it is not clear whether a cognitive test battery is superior to the MMSE or not. Despite the advantages of the MMSE, it is important to note that some people who were not considered as having dementia according to the consensus conference had an MMSE score below the cut-off. Likewise, about one-third of the persons diagnosed with dementia had an MMSE score above the cut-off. Thus, the MMSE is not an optimal proxy for dementia in research, and a positive screening should not be considered as a definite diagnosis but as an indication that the clinician should undertake a diagnostic follow-up. This caution probably also applies for other short screening tests.[181] A low score on the MMSE may be related to other factors, such as depression, old age, low educational level, somatic diseases, and the consequences of stroke.[182-184] High scores on the MMSE despite the onset of early dementia might be the result of a person's having a higher education and thus being better able to compensate for cognitive shortcomings.

We could not confirm that the 10th percentile of any cognitive test evaluated in the present study is a good proxy of dementia. The sensitivity for single tests was low, as was the PPV, meaning that persons diagnosed with dementia scored above the cut-off and persons not diagnosed with dementia scored below it. Higher drop-out rates among persons with dementia might be one explanation for the low agreement values. Another explanation is that cognitive tests are in general designed to capture small changes; hence, they also become sensitive for other factors that might affect

cognitive test results. However, the assessment of various cognitive domains is a central and important issue in differential diagnoses,[185] especially when they are qualitatively evaluated.

The research nurses correctly identified about four out of five persons with dementia, with few false positives. The nurses had estimated each respondent's ability to behave, function, and perform tests in their ordinary environment. Results show that a four-hour IPT, including the MMSE combined with a cognitive battery in each respondent's home, gives a good picture of their mental status. To our knowledge, this has not been examined before. The fact that both medical records review (i.e., physician knowledge about dementia) and nurse evaluations yielded the highest agreement values underscores the importance of personal interaction in dementia diagnoses.

Identifying rates in medical registries primarily relies on physician knowledge and willingness to evaluate and disclose a diagnosis and then enter it correctly into a registry, which might be considered time consuming. As seen in the present study, physicians were aware of memory problems in most cases, but only one out of two persons with dementia had received an explicit dementia diagnosis. Of these, every other person appeared in the IDR. In a study from Italy, less than 50% of the persons with a dementia diagnosis were identified by a dementia registry, and older persons with dementia were less likely to be included in the registry.[51] A study on the reliability of registry data from the STR, including data from the SATSA and OCTO-twin study, reported that 55% of prevalent patients were identified by the IDR.[50] The lower identification rate in our study compared with this other study from STR might arise from a delay between dementia onset and appearance in the IDR, as also shown by Jin and colleagues.[50] Dementia diagnoses appeared in the IDR on average five years from onset of disease. Moreover, the participants in the Gender Study were on average younger than participants in the SATSA/OCTO-twin study and hence less likely to have had been diagnosed with dementia during a longer time period. Interestingly, some of the patients were identified as having

dementia by the IDR but not by the consensus group. This inconsistency may arise from the higher drop-out rate among persons with dementia. In fact, most of these cases were recorded as being dementia in the IDR after they had withdrawn from the present study. However, it seemed as though some people had either been wrongly identified with dementia or that the IDR coding had failed. A Danish study showed that about 85% of those who appeared in the Danish Hospital Registry were correctly diagnosed with dementia, leaving 15% who had been incorrectly diagnosed.[186]

Strengths and Limitations

The most critical issue in studies comparing agreement among varying sources is the validity of the source considered to be the gold standard: In the present study, this source was the dementia diagnosis from the consensus conference. The total research protocol including all tests analyzed in the present study, except the diagnoses from the IDR, was evaluated during the consensus conference. Even though the research protocols were extensive, longitudinal, and developed to identify persons with dementia, it should be noted that a clinical evaluation with the possibility of ordering blood samples, brain imaging, etc., would have been even better. The medical records, MMSE, Block Design, and nurse evaluations on the Berger scale were selected as inclusion criteria for the consensus conference. It is likely that the members of the consensus conference considered these measures more important than other measures. Accordingly, these tests yielded the highest agreement values. However, the effect of a single source ought to have been diminished because several sources from an extensive research protocol were used and not only the tests evaluated in the present study. For example, in the evaluation of cognitive test scores, information about educational level, occupation, and prevalence of depression (both available from the research protocol and medical records) were considered. Moreover, because the participants in the Gender Study were evaluated three times during an eight-year period, a single value was of less importance compared to the cognitive development.

5.3. Midlife Body Mass Index and General Cognitive Ability in Late Life

Knowledge about the impact of midlife overweight on cognitive abilities is of critical importance because overweight is becoming more and more common. We found that persons with higher BMI scores in midlife had an increased risk of lower general cognitive ability in late life, and that these overweight men and women also had a steeper decline in this ability. The association remained when persons diagnosed with dementia at any time during the study period were excluded from the analysis. Hence, midlife overweight might influence cognitive functioning independently from dementia.

Few comparable studies have evaluated the association between midlife BMI and cognitive abilities in late life, and to our knowledge, no previous study has controlled for dementia. Thus, although both the Whitehall II Study[121] and the Framingham Offspring Study[122] have several strengths, it cannot be excluded that the association seen between overweight and cognitive deficits in executive functioning and memory were the result of dementia. Neither can the results from the Framingham Heart Study be compared to the present study because they assessed BMI in late life.[140,141] The time point of BMI assessment seems to be relevant because several studies have reported that midlife high BMI is associated with a higher risk of dementia,[79,113,115,116] while in late life, high BMI scores or excess weight are in most studies associated with a decreased risk of dementia.[120,125,127,130-133] It should be noted that despite the extensive evaluation of dementia in the present study, we do not entirely rule out the possibility that those individuals who experienced more rapid cognitive decline were in the preclinical stages of dementia. Because SATSA is an ongoing project, future studies can address whether the association between higher midlife BMI scores and lower general cognitive ability result from preclinical dementia or not.

Strengths and Limitations

The main strengths of our study include its population-based design, the long follow-up time with repeated evaluations of cognitive function using a battery of cognitive tests, and a midlife perspective of CVD and lifestyle factors. A composite cognitive outcome measure has several advantages over single measures of cognitive function; for example, composite measures reduce the sources of measurement error such as different difficulty levels and floor and ceiling effects.[30] However, a composite score assesses only a general ability and not decline in different cognitive domains. We will in future studies evaluate the association between midlife BMI scores and a variety of cognitive domains. Although the long follow-up time is a strength of the study, it might also underestimate the rate of cognitive decline because the participants at baseline are better cognitively from the beginning, and the participants who complete follow-ups are a further selection of these.[187,188] Some of this effect is diminished with latent growth curve modeling because persons with one measuring point are included in the analyses but more weight is given to those persons with more measurement occasions.

It should also be mentioned that the proportions of participants in this study who were obese were relatively low, but the proportions of persons who were obese in this study seemed to be representative of the estimated proportions in the Swedish population in the 1960ies and 1970ies.

5.4. Overweight in Late Life and Dementia Risk

Both low and high late-life BMI scores have been proposed to be associated with an increased dementia risk, but most studies including the present work support an association between low BMI and greater dementia risk in old age.[120,127,130-133] We found that for each unit decrease in BMI scores at baseline, the risk of dementia increased by 8% over eight years. This estimate is pretty similar to those reported from other studies that primarily included White participants,[120,129,132] while in the Kame Project that included only Japanese-Americans, the estimated risk of AD was much higher at 44% for each unit decrease in BMI.[130]

To exclude the possibility of reverse causality in the present study, we excluded persons who developed dementia during the first four years of follow-up. This exclusion did not change the results substantially, as also was reported in the Religious Order Study.[129] Despite this lack of change, the possibility of a reverse causality in the present study and the studies referenced above cannot be excluded because lower weight has been reported 10 to 20 years before the clinical onset of dementia.[125,126] In addition, declining weight and BMI scores have been associated with the preclinical phase of dementia.[120,125,127-133] Even if our results show that persons diagnosed with dementia had lost more weight between baseline and follow-up than those not diagnosed with dementia, we could not evaluate the decline in BMI before dementia onset because BMI was assessed only at the follow-up and not at the time of dementia onset.

The processes that cause people with preclinical dementia to lose weight are complex and not well understood. It has been proposed that olfactory functions decline in MCI[189,190] and AD,[191] and accordingly, food becomes less appetizing. A couple of studies have shown that the limbic system, which regulates appetite, is affected in patients diagnosed with AD.[192,193] Moreover, forgetfulness and loss of initiative, which are common in the preclinical stages of dementia, might lead to malnutrition. Although many researchers believe that the association between low BMI scores and greater dementia risk is due to preclinical dementia,[110,124,129] there are also potential biological mechanisms associated with overweight that might be beneficial for brain functioning. For example, both the hormones leptin and estrogen are produced in the adipose tissue, and both are associated with better cognitive functioning.[139,194]

However, as already noted, previous research is not conclusive, and an increased risk of dementia with higher BMI scores in late life has been reported,[134,135] as have U-shaped associations.[127] The H70 study reported that high BMI in late life was associated with an increased risk of AD among women (no separate analyses were

performed on men because of the small sample size),[134] while in the Cache County Study, obesity increased the risk of AD in females but not among men.[135] The association of high BMI scores and the risk of AD found in the H70 study could be the result of the long follow-up time because the adverse effects of overweight are considered to be delayed.[11] However, this rationale does not explain the association seen between higher BMI scores and dementia in the Manhattan Study[127] and in the Cache Count Study,[135] in which the follow-up times were shorter than in the present work. Factors contributing to these differences remain to be elucidated.

Low BMI scores were a stronger risk factor among women compared with men in the Lieto Study. The same pattern was found 11 to 20 years before dementia onset in the Rochester Epidemiology Project, a longitudinal prospective study.[126] In the prospective Health Aging Body Composition Study including persons with dementia, high levels of adiposity measures were associated with greater cognitive decline among men, but higher adiposity measures were associated with less cognitive decline in women over a 7-year period.[142] However, in other studies like the longitudinal Rancho Bernardo Study, both men and women diagnosed with dementia had lost at least 5 kg more than cognitively intact persons over a 20-year period before dementia onset,[136] and no gender differences were found in the Religious Order Study.[129] These contradictory findings point to the importance of analyzing men and women separately.

It has been proposed that the sex differences observed in the relationship between BMI score and dementia onset might be the result of hormonal factors and social and behavioral differences.[126] Differences in the amount of fat among men and women with the same BMI score might also blur the associations between BMI and dementia risk in late life. We think that some methodological aspects also may explain the difference seen between men and women in the present study. There is a strong selection bias for women in all population-based studies in older persons because women live longer than men, and women also live longer with dementia.[195] Thus, the numbers of older men and the numbers of elderly men with dementia are

smaller, which lowers the power in gender-stratified analyses of elderly men. The same problem with power might hold for the analyses in the two different age groups, in which the association between low BMI scores and dementia reached significance in the older age group, but not in the younger. Fewer persons in the younger age group were diagnosed with dementia; thus, the results from subgroups should be interpreted with caution.

Strengths and Limitations

It is well known in epidemiological studies that persons with dementia drop out from studies at a higher rate than their cognitively intact counterparts because of death or an inability to participate, which might affect the interpretation of the present results. Among those that dropped out after the first IPT in the Lieto Study, 13.1% had been diagnosed with dementia according to the official Finnish Cause of Death Registry, similar to the prevalence rate of dementia in the present study. However, as earlier shown in this thesis, registry data likely underestimate the prevalence of dementia. Hence, if there is a true association between low BMI scores in late life and a greater dementia risk, this study might underestimate the association because those who had died and/or dropped out had lower mean BMI scores at baseline. Another important feature of this study, which needs to be considered in the interpretation of the results, is that the mean BMI for the present Finnish sample is higher than that reported for comparable studies of the same age groups in Canada,[196] France,[131] Sweden,[132,175] and Taiwan,[197] but similar to mean BMI scores reported from the United States.[129] In the present study, BMI scores relied on clinical anthropometric assessment, so any misclassification bias due to under- or overestimation of height and weight was not present; however, other anthropometric measures that better differentiate between muscle and fat mass would of course have been of interest, if they been available.

5.5. General Discussion

5.5.1. Possible Causal Pathways between Overweight and Lower Brain Functions

An increasing body of evidence points towards an association between overweight in midlife and lower brain functioning in late life. The causal pathways largely remain unknown, but several have been proposed and are reviewed briefly below.

Lifestyle Factors

High BMI scores are in most cases the result of an unhealthy lifestyle, such as absence of exercise and a high-calorie diet. Exercise in both midlife and late life has been associated with better cognitive abilities and less risk of dementia.[99,100,104-108] Thus, it is hard to sort out whether obesity is the cause or an intermediate step on the causal pathway.

Figure 5. Possible Causal Pathway between Overweight and Cognitive Impairments and Dementia.

Cardiovascular Diseases

The assumption that CVD may be on the causal pathway between overweight and cognitive impairment and dementia is not very surprising: Overweight persons have an increased risk of various states causing CVD and/or CVD, and these states have been linked to an increased risk of dementia.[69,70,72,73,75,198] Atrial fibrillation, congestive heart failure, and coronary artery disease cause hypoperfusion in the brain, which leads to neuronal death.[198] Studies on midlife BMI and late life brain health usually control for most of these conditions. In some studies, the association becomes weaker or non-significant when CVD is controlled for,[119,120] but not in others,[116,117] as was the case in our study on midlife BMI and cognitive ability in late life. Overweight, CVDs, and related states are closely associated with each other, and the development of these conditions is considered to reflect a common underlying pathology. On an individual level, all disorders associated with MetS have to a

certain extent been recognized as risk factors for cognitive decline and dementia.[79,199,200] Whether the sum is greater than its parts remains to be determined, but synergistic effects on cognitive functioning have been reported for various risk factors, such as waist–hip ratio and hypertension,[122] and hypertension and diabetes.[201] Taken together, the increased risk of CVD among overweight persons is almost certainly on the causal pathway between overweight and poorer brain health. However, it is not likely that this is the only possible pathological pathway.

Hormones

Adipose tissue is the body's largest endocrine organ and secretes hormones, cytokines, and growth factors, which can cross the blood–brain barrier[202] and affect brain health. Likewise, these factors can interact directly with blood vessels[203,204] and contribute to homeostasis. Leptin and adiponectin have been suggested as possible pathways between overweight and brain health,[205] with leptin, an important factor in eating behaviors and energy expenditure, having important implications for memory processing.[194]

Inflammation

Overweight persons have higher levels of inflammation than normal-weight persons.[206] Several case-control studies have also shown increased levels of sCRP among persons with dementia,[207-211] and acute-phase reactants such as sCRP and pro-inflammatory cytokines like IL-6 have been seen in amyloid plaques and neurofibrillary tangles in the brains of patients with AD.[212] In longitudinal studies, sCRP has been associated with cognitive decline[80,81] and increased risk of dementia, even when BMI is controlled for.[213,214] Unfortunately, inflammation markers from midlife were not available in SATSA. The risk of cognitive decline is higher among persons with both MetS and elevated levels of sCRP.[80] Further support for the association between inflammation and lower cognitive abilities is that the use of NSAIDs lowers the risk of dementia and cognitive decline, especially if started in midlife and over an extended period of time.[83-85] However, randomized control trials with NSAIDs among persons with AD have not been successful.[215,216]

Diabetes

It is well known that being overweight confers a substantially increased risk of type 2 diabetes. Various meta-analyses have shown that persons with type 2 diabetes have an increased risk of cognitive impairments and dementia,[72,73] and especially a greater risk of VaD.[217,218] Learning and memory seem to be especially affected, but deficits attributable to diabetes have been shown in more or less all cognitive domains,[73,219,220] except short-term memory.[220] Prediabetes states, like decreased insulin sensitivity and hyperglycemia, have also been associated with an increased risk of dementia[221] and lower cognitive test performance.[222,223] Hence, defects in insulin action and elevated glucose levels might be one possible link between overweight and impaired cognitive health. Adding diabetes to the model did not change the association between midlife BMI and cognitive ability substantially in the present study. Some studies on midlife BMI and dementia report an attenuated association when diabetes is included,[119] whereas others do not.[114] In the Framingham Heart Study, there was no interaction between obesity and diabetes on cognitive performance, while both independently had a negative effect on cognitive performance among men.[141] The pathological pathways from overweight and diabetes to cognitive impairments and dementia might differ.[141]

Which Comes First?

Most studies in this research field, including SATSA, do not assess cognitive abilities in midlife but only at follow-up. With these designs, it cannot be ruled out that the association between overweight and low cognitive functioning could have been present long before a person enters into late life. A couple of cross-sectional studies have shown that high BMI scores in midlife are associated with lower cognitive abilities,[224,225] whereas BMI was only weakly inversely associated with intelligence among 1 million Swedish men around the age of 18 years.[226] Prospective studies have shown that low cognitive functioning in childhood predicts obesity[227,228] and type 2 diabetes in midlife.[229] Likewise, low intelligence in young adulthood has been associated with MetS and higher blood glucose levels in midlife.[230] Several of these studies suggest that these associations are attenuated when educational attainment is considered, probably in part because educational

level correlates with cognitive abilities. Thus, controlling for educational attainment, as done in study III, might to some extent control for comorbid cognitive abilities and support the notion that overweight in midlife predicts lower cognitive ability in late life. Moreover, the finding that higher BMI scores in midlife predict a steeper decline in general cognitive ability in late life also indicates that BMI is the exposure and not the outcome. However, this association needs to be further explored in studies with a lifetime approach.

5.5.2. The Shift in Association

With few exceptions, most studies show that the relationship between overweight and future brain functioning in older persons differs from that between midlife BMI and brain functioning in late life, including studies following the same cohort.[120,125] There are several possible explanations for this shift. In old age, there is a selection bias for people who have survived until late life, often called the "hardy survivors." These persons yield a cohort of elderly survivors who might be less susceptible to the health problems of being overweight than those who did not survive, or these survivors might be carriers of benign forms of overweight not associated with insulin resistance and atherosclerosis.[231,232] In the Lieto study, only 11.9% of the obese participants had diabetes mellitus, a comparatively low rate of diabetes among obese populations. Moreover, in late life, overweight might be a nutritional reserve for the individual in times of illness or trauma. Persons with higher BMI scores are more likely to survive illnesses; for example, overweight persons with a diagnosis of heart failure have a better prognosis than underweight and normal-weight persons with heart failure.[233] However, and maybe most important, in late life, low BMI scores might be a manifestation of metabolic changes arising from preclinical dementia.

5.5.3. Methodological Considerations

Body Mass Index

Even though BMI is strongly correlated with total body fat,[12,13] there is considerable variability in the body composition for people with the same BMI scores.[234] Some

people with low BMI scores have as much fat as those with high BMI scores,[234] and women have more fat than men with the same BMI scores.[12,13] To account for gender differences, analyses have either been carried out separately for each gender or gender has been added to the models and allowed to interact with other variables of interest. However, in this thesis, we found no main gender differences in the association between BMI and brain health. Another limitation with BMI is that it does not distinguish between different types of fat. It is well known that waist circumference, a better predictor of intra-abdominal fat than BMI, is also a stronger predictor of CVD than BMI, and to a higher extent correlated with, for example, insulin resistance.[235] Accordingly, it has been reported that central obesity in midlife is a better predictor of dementia than BMI,[112,115] while studies on dementia risk with various anthropometric measures in late life have been inconlusive.[127,130,142] Unfortunately, neither waist circumferences nor any other anthropometric measures were available in SATSA or the Lieto study at baseline.

The optimal cut-off scores for BMI for the elderly have been discussed.[236] WHO's cut-off scores have been criticized as being insensitive to detecting adiposity in late life because with increasing age, muscle mass decreases while fat mass increases.[234] However, the cut-off scores have also been criticized as being too restrictive because being overweight in late life does not seem to be associated with an increased mortality risk.[236] To avoid misclassification bias, all main analyses in the present thesis have been performed with BMI as a continuous variable. The samples have only been divided into different BMI categories for descriptive purposes, and because there are no generally accepted cut-off scores for the elderly, the standard WHO definitions of normal weight, overweight, and obesity have been used. Further support for the usefulness of these cut-off scores comes from a study of more than 1 million adults in the United States, where the optimal BMI scores ranged from 20.5–24.9 for all age groups,[237] close to what is considered as not being associated with an increased health risk according to WHO (18.5–24.9).[15] It is, however, still possible that BMI values between 18.5–24.9 should not be considered

normal among elderly because a substantial part of the aging population has a BMI above these limits.[175]

Dementia Diagnoses

In all studies, dementia was screened for in several ways, by the MMSE, medical records review, indications during the interview, or other tests of interest. The wide screening and the extensive research protocols used for diagnoses are strengths of this thesis. Educational level, socioeconomic status, and prevalence of depression were considered. Especially, strengths are the longitudinal design of the Gender Study and SATSA with repeated measures of a range of cognitive abilities because the likelihood of people with low baseline cognitive capacity being mixed up with persons with dementia is much lower than if cognitive abilities are assessed only once. However, clinical diagnoses with the possibility of ordering specific tests would have been preferable, as was done in the Lieto Study.

Generalizability

No study is completely representative of a population, and this should be kept in mind when conclusions are drawn from this and other studies. The problem with generalizability in the current study is similar to that for all other studies of the elderly. There is a selection bias for healthy old people because unhealthy elders, including those with cognitive impairments and dementia, are less likely to be willing or able to participate. Unhealthy persons are also more likely to drop out earlier from studies. In analyses of the STR, Pedersen et al. have shown, as expected, that the non-responders are unhealthier in midlife than the continuing sample.[238] This scenario might lead to an underestimation of the negative effect of BMI on global cognitive ability.

Participants in the SATSA study and the Gender Study includes twins living all over Sweden. The generalizability of twin studies to non-twin populations is sometimes questioned. We consider this to be a minor problem because several studies have shown that the population of twins included in the STR does not differ from the Swedish population in general.[239] Neither do the twins reared apart

differ from the twins reared together, except that the twins reared apart had lower socioeconomic status in childhood.[240] Among elderly twins, Simmons et al. found no main differences in health status or biobehavioral functioning between twins and non-twins.[241] In the analyses on BMI and cognitive functioning, in which greater similarity within the twinpair can be expected because of high heritability, twinness has been controlled for. Hence, the results from SATSA can most likely be generalized to the general population.

The results from the Gender Study can probably be generalized to the general Swedish population, but due to differences in health care systems and education of general practitioners, the accuracy of sources like registries and medical records might differ between countries. Because the participation was high in the Lieto study and the participants had living conditions similar to those of the Finnish population in general, except for overrepresentation of agricultural occupations,[242] the results can probably be generalized to the general Finnish population, and especially to semi-rural areas.

6. Conclusions

In old age, there is a small but significant increase in the mean difference between self-reported and measured BMI, likely because of a lack of awareness about changes in height over time. No linear increase in misclassification bias was found for weight. As the increase in misclassification bias for BMI is very small, self-reported BMI can probably be used as a continuous variable in longitudinal studies whit out affecting the results.

Medical records and evaluations by experienced research nurses, respectively, are valuable instruments in identifying persons with dementia in an elderly population. MMSE scores might also be useful, as long as they are interpreted with caution. In this age group, cognitive test results below the 10^{th} percentile were not equivalent with dementia and should probably not be used as a proxy of dementia in research. Studies relying exclusively on dementia identification from registry-based data will, at least currently, underestimate the prevalence of dementia.

Persons with high BMI scores in midlife are at a higher risk of lower cognitive ability and steeper cognitive decline in late life, even among persons who are not affected by dementia. Moreover, the association between BMI in midlife and late life cognitive development does not seem to be mediated by an increased risk of CVDs, implying that nonvascular pathways might be involved in the development of dementia.

High BMI scores in late life are not associated with an increased risk of dementia. Persons who subsequently are diagnosed with dementia have lower BMI scores about a decade before clinical onset of dementia than persons who do not develop dementia. In clinical practice, low BMI scores might be an early indication of dementia.

7. Relevance and Implications

Detecting factors leading to cognitive impairments in old age is of great importance to public health. This thesis shows that persons with higher BMI scores in midlife are at a higher risk of lower cognitive ability in late life. Given the increased burden of overweight and obesity in Western societies, this thesis is of great relevance, showing that overweight not only increases the risk of dementia but also extends to cognitive functioning in a dementia-free sample. Because the prevalence of overweight and obesity have increased steadily over the last decades, the prevalence of cognitive impairments and dementia might become more common in the oldest age groups, if these persons do not die of other obesity-related complications. The shift seen in old age, in which high BMI scores go from being a risk factor for dementia to a protective factor, points to the importance of not generalizing findings from younger age groups to older age groups. Health advice customized for elderly persons needs to be developed.

Validity and reliability of both outcome measures and predictors are of great importance in all research. This study shows that self-reported BMI is a fair measure in old age, and self-reported weight seems to be more reliable than height. Review of medical records and nurse evaluations (after a four-hour IPT in each respondent's home) both yielded high sensitivity and specificity and could be used as proxy for dementia, even if the prevalence rate will be underestimated. If the MMSE is used, it should kept in mind that even if it captures around 70% of all persons with dementia, it also includes a number of persons without dementia. Studies using only registry data to identify persons with dementia should be interpreted with caution.

8. Future Directions

An increasing body of evidence links BMI in midlife with an increased risk of dementia in late life. However, we are among the first to evaluate the association between BMI in midlife and cognitive development in late life, and to our knowledge, the first to study the association in a dementia-free sample. Future studies need to confirm these findings and evaluate the association between midlife BMI and various cognitive domains. Other measures of adiposity taking fat distribution into account are also required. Because low cognitive abilities can be an early sign of dementia, samples need to be followed until death, preferably in combination with brain imaging and autopsy.

Although several studies confirm our findings regarding the association between low BMI in late life and a greater dementia risk, there are inconsistencies. Better measures of adiposity, which differentiate between malign and benign forms of adiposity, might be a key factor in understanding the association between adiposity and dementia risk in late life. There is also lack of knowledge about sex differences and the association with various forms of dementia. Studies with greater sample sizes need to address these questions.

The shift and timing of the shift when overweight goes from being a risk factor to a protective factor of dementia are not well understood. Studies including lifestyle factors, comorbidities, biomarkers, and genes, ranging over the whole life span, preferably from *in utero* to death, could lead to a better understanding of both the shift and its causality. Because the prevalence of overweight is expected to increase, there is a great need to understand the underlying mechanisms linking overweight to cognitive decline and dementia so that prevention programs and treatment strategies can be developed.

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