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UNRAVELING THE RELATIONSHIP BETWEEN BODY MASS INDEX AND CARDIOMETABOLIC DISEASE, DEMENTIA, AND SURVIVAL IN OLD AGE

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Unraveling the relationship between body mass index and cardiometabolic disease, dementia, and survival in old age
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To my family

ABSTRACT

Overweight and obesity, commonly defined as a body mass index (BMI) ≥25 kg/m^2, affect more than half of older adults. However, the relationship between BMI and health outcomes in old age are unclear. This PhD project aims to describe the trajectories of BMI alongside other anthropometric measures in old age. Additionally, this thesis explores the associations between short- and long-term changes in BMI with cardiometabolic diseases (CMDs), dementia, and survival, highlighting modifiable factors that could modify such associations. Longitudinal data from the Swedish National study on Aging and Care-Kungsholmen (SNAC-K) and the Screening Across the Lifespan Twin study (SALT) were used.

Study I. We assessed long-term trajectories of BMI, calf circumference (CC), and mid-arm circumference (MAC) and identified factors associated with these trajectories among older adults from SNAC-K. BMI, CC, and MAC declined significantly over the 15-year follow-up. CC and MAC, proxies of muscle mass, declined earlier and more steeply than BMI. More pronounced declines of the three anthropometrics were observed in participants aged ≥78 years of age than those <78 years of age. Moreover, cardiometabolic disorders (including diabetes, heart disease, stroke, and hypertension) accelerated the rate of these declines, whereas high educational attainment and physical activity appeared to attenuate them.

Study II. We investigated the associations of BMI and its long-term change (over 25−35 years) with CMDs (including diabetes, heart disease, and stroke) in Swedish twin individuals aged >40. Participants with high BMI (≥25 kg/m^2, including overweight and obesity) had a higher risk of any CMD (hazard ratio [HR] 95% confidential interval [CI] = 1.52 [1.45−1.58]) and cardiometabolic multimorbidity (having ≥2 CMDs; 1.93 [1.76−2.13]) than those with normal BMI (20−25 kg/m^2). The BMI-CMD association was independent of familial factors. A favorable lifestyle could partly mitigate the impact of high BMI on CMDs. Moreover, having high BMI only earlier (1.28 [1.02−1.59]) or later in life (1.33 [1.24−1.43]) was still associated with an increased risk of CMDs compared to having a consistently normal BMI. Those with a high BMI both in earlier and later life had the highest CMD risk (1.69 [1.55−1.85]).

Study III. We examined the association between BMI change over 6 years and subsequent incident dementia in the SNAC-K cohort. There was a U-shaped association between BMI change and dementia risk. Participants with large BMI change (>10%) had a higher dementia risk than those with stable BMI (change ≤5%) (for large BMI loss, HR [95% CI] = 2.93 [1.72−4.91]; for large BMI gain, 2.61 [1.09−5.54]). Compared to *APOE* ε4 non-carriers with stable BMI, dementia risk was higher among *APOE* ε4 carriers with a large gain (9.93 [3.49−24.6]) or loss (6.66 [2.83−14.4]) of BMI.

Study IV. We assessed the impact of mid- and late-life high BMI (≥25 kg/m^2) on overall survival and chronic disease (including diabetes, heart disease, stroke, and cancer)-free survival in Swedish twins aged 60 to 79 years. Older adults with high BMI had 1.4 (95% CI 0.6−2.2) years shorter disease-free survival than those with normal BMI, though their overall survival was similar. Participants with consistently high BMI from mid- to late-life and those with high BMI in mid- but not late-life had 2.2 (95% CI 1.0−3.4) and 2.6 (95% CI 0.7−4.4) years shorter chronic disease-free survival, respectively.

Conclusions. BMI, together with CC and MAC, declines over time in older adults. High BMI in mid or late life is associated with an increased risk of CMDs, and a large change of BMI in old age is related to dementia risk. Moreover, a high BMI in mid or late-life may shorten chronic disease-free survival. Together, these findings suggest that mid or late-life high BMI and largely changes in BMI may predict adverse health outcomes in old age.

Key words. body mass index, calf circumference, mid-arm circumference, trajectory, cardiometabolic disease, lifestyle, dementia, disease-free survival

LIST OF SCIENTIFIC PAPERS

I. **Guo J**, Shang Y, Fratiglioni L, Johnell K, Welmer AK, Marseglia A, Xu W. Individual changes in anthropometric measures after age 60 years: a 15-year longitudinal population-based study. Age Ageing. 2021 Sep 11;50(5):1666-1674. doi: 10.1093/ageing/afab045.

II. **Guo J**, Li X, Yang R, Marseglia A, Dove A, Johnell K, Xu W. Association of body mass index and its long-term changes with cardiometabolic diseases: A nationwide twin study. Clin Nutr. 2021 Nov;40(11):5467-5474. doi: 10.1016/j.clnu.2021.09.030.

III. **Guo J**, Marseglia A, Shang Y, Dove A, Grande G, Fratiglioni L, Xu W. Association between late-life weight change and dementia: A population-based cohort study. J Gerontol A Biol Sci Med Sci. 2022 Aug 3:glac157. doi: 10.1093/gerona/glac157.

IV. **Guo J**, Dove A, Shang Y, Marseglia A, Johnell K, Rizzuto D, Xu W. Associations between mid-to-late life body mass index and chronic disease-free survival: A nationwide twin study. Under Review

CONTENTS

LIST OF ABBREVIATIONS

APOE	Apolipoprotein E
BMI	Body mass index
CC	Calf circumference
CI	Confidence interval
CMD	Cardiometabolic disease
CVD	Cardiovascular disease
ELECT	Estimating Life Expectancies using Continuous Time
HbA1c	Glycated hemoglobin
HR	Hazard ratio
ICD	International Classification of Diseases
MAC	Mid-arm circumference
MMSE	Mini-mental state examination
NPR	National Patient Register
OR	Odds ratio
RCT	Random clinical trial
RERI	Relative excess risk due to interaction
SALT	Screening Across the Lifespan Twin study
SD	Standard deviation
SNAC-K	Swedish National study on Aging and Care-Kungsholmen
STR	Swedish Twin Registry
WHO	World Health Organization

1 INTRODUCTION

1.1 Population aging

Globally, population is aging more rapidly than ever before, with the proportion of people over the age of 60 increasing from 12% in 2015 to a projected 22% in 2050 (1). In the past two decades, worldwide life expectancy at birth has increased from 67.2 years in 2000 to 73.5 years in 2019 as consequence of improved living conditions and advances in healthcare (2). Increased lifespan gives older people the opportunity to contribute more to their families and society using their accumulated experience and knowledge. However, the extent to which older people can fulfill their potential and benefit from extended longevity largely depends on the quality of their social, mental, and physical health. For some individuals, living longer can come at the cost of suffering from multiple chronic diseases and physical disabilities. The Global Burden of Disease Study reported an increasing number of years spent in poor health from 1990 to 2019 (8.5 to 10 years), which may offset the advantage of improved life expectancy during the same period (67.2 to 73.5 years) (2). In the context of our aging population, it is important to identify and thus modify risk factors for adverse health outcomes in old age in order to extend the proportion of life lived in good health.

1.2 Overweight and obesity

Overweight and obesity, defined as abnormal or excessive fat accumulation, result from an imbalance between energy intake and energy expenditure. Conventionally, a body mass index (BMI) over 25 kg/m^2 indicates overweight, and a BMI over 30 kg/m^2 constitutes obesity (3). The prevalence of overweight and obesity has risen steeply over the past decades, reaching epidemic proportions: in 2016, 39% of adults aged ≥18 years worldwide had overweight, and 13% had obesity (4). Overweight and obesity are leading risk factors for numerous chronic diseases. Excessive adipose tissue can increase insulin resistance (5), enhance free fatty acid turnover (5), and introduce systemic inflammation (6), all of which contribute to the development and progression of cardiometablic disorders such as type 2 diabetes (hereafter, diabetes), hypertension, and cardiovascular disease (CVD) (5,6). Beyond cardiometabolic disorders—which may involve the same metabolic pathways as adiposity—overweight/obesity has also been associated with an increased risk of non-metabolic diseases, such as cognitive impairment and dementia (7). These adverse health outcomes could lead to limitations in physical function (8) and eventually disability (9), reduced quality of life (10), and increased risk of premature mortality (11). Despite the efforts of health care systems to prevent and treat obesity, it remains one of the most significant increasing risk factors contributing to the global burden of disease (12).

Overweight and obesity in old age. Overweight and obesity are more common in older age. In the European population, 42.4% of adults aged ≥60 years are overweight and 20.9% are obese, compared to 40.0% and 17.1% of middle aged adults, respectively (13). While early- or mid-life high BMI (i.e., BMI ≥25 kg/m^2, including overweight and obesity) has been well-established as a health risk factor, the consequences of high BMI in late life are unclear. Some studies have shown no association or even a negative association between overweight/obesity and adverse health outcomes (14–16). The inconsistent associations between high BMI and health outcomes may arise from the limited ability of BMI to

differentiate between fat mass and muscle mass. Fat mass is the primary source of BMI variation in young and middle age (17). In old age, however, BMI loss may be driven by muscle mass loss due to aging per se, malnutrition, or underlying adverse health conditions. Normal BMI may also represent a heterogeneous entity and reflect different risk profiles. For instance, some individuals with normal BMI may be at a higher disease risk if they have excessive fat mass accompanied by low muscle mass. Moreover, the disease risk associated with an individual's current BMI value may vary according to their previous BMI status. People with a normal BMI but a history high BMI may have greater disease risk relative to those with a consistent normal BMI (18–20). Therefore, it is essential to account for the enduring effects of early-life obesity in the older population. The unclear relationship between BMI and health outcomes among older adults raises challenges for managing and preventing geriatric overweight/obesity. Estimating lifetime BMI profiles and BMI trajectories may help enhance the utility of BMI as an indicator in geriatric health practice.

1.3 Trajectories of body compositions in aging

Body composition changes with aging. In healthy individuals, fat mass increases from the age of 20, reaching a plateau in older age (that is, approximately between ages 70 and 80), and decreasing slightly after the age of 80. Muscle mass increases between ages 20 and 50 and then steadily decreases at a non-linear rate with aging (17,21). Changes in both fat and muscle mass can contribute to BMI changes over the life course. In young adults, most of the variation in BMI is due to changes in body fat mass (22). However, in older adults, a decline in BMI often reflects the loss of muscle mass rather than fat mass (23,24). Emerging evidence has shown that progressive muscle mass loss is associated with various adverse health outcomes in late life (25,26).

Concerns about using BMI decline to indicate muscle mass loss in older adults still exist. Muscle mass loss may occur and be masked by a simultaneous increase in fat mass among those who show a stable or slightly increased BMI over time (27). Several studies have investigated the accompanying changes in BMI and muscle mass in older adults (28–31). These studies consistently reported that muscle mass declines over time. However, the pattern of BMI change was unclear. Some studies reported a non-significant change or slight increase in BMI (28,29,32,33), while others detected a decline in BMI over time (30,31). The heterogeneity of previous findings may be due to methodological differences. Age of study participants is one important consideration. There is a turning point in fat mass around age 70 to 80 years, after which fat mass stabilizes or slightly declines. Thus, in very old adults, it is reasonable to speculate that BMI change is more likely to reflect changes in muscle mass rather than fat mass (17). However, previous studies either included only younger-old adults or failed to perform analyses by age groups (e.g., based on the turning point in fat mass trajectory) given limited sample sizes (23,33). Moreover, some of the studies had a cross-sectional design (29,30), and birth cohort effects may distort the age-related changes in body composition. Therefore, more well-designed longitudinal studies with a longer follow-up and wider range of age groups are needed to explore and compare the trajectories of BMI and muscle mass.

Notably, loss of muscle mass over time is mainly due to the loss of appendicular muscle mass (i.e., the sum of the muscle mass of the four limbs) (28). Calf circumference (CC) and mid-arm circumference (MAC) have been proposed to be proxies of muscle mass (34,35). Indeed, CC and MAC may partially reflect fat mass, but with aging, fat mass is more likely to redistribute from the limbs to the trunk (36). In this manner, the loss of muscle mass in the arms and legs would not be masked by increased fat mass. However, to our knowledge, no previous study has explored the trajectories of CC and MAC and compared them with BMI change in older adults.

Determinants for the change in body compositions. Because of the critical implications of weight or muscle mass loss in the development of age-related diseases, there is a growing interest in identifying the potentially modifiable factors (e.g., lifestyle) that can prevent, or at least attenuate, such losses. Observational studies have shown that being physically active is associated with slower weight loss among older adults (37,38). In a review including 34 randomized clinical trials (RCTs), 27 reported a beneficial effect of physical activity on muscle mass loss in individuals aged 60 years and older (39). Studies that failed to observe such benefits were more likely to be targeted at people with frailty or limited mobility who may have low adherence to the physical activity intervention (39). Moreover, previous literature has shown that chronic health conditions (e.g., coronary heart disease and diabetes) may accelerate the decline in weight or muscle mass in aging (40–43). For example, in the Health, Aging and Body Composition study, among adults aged 70–79 years with undiagnosed and diagnosed diabetes, muscle mass declined at a rate of 0.34 and 0.22 kg/year, respectively (vs. 0.20 kg/year for those without diabetes) (40). Older adults with vascular disorders also showed significant muscle loss (41,44). Given the growing health concerns about weight or muscle mass loss among older people, it is important to better understand the factors associated with the progression of these losses. Previous studies exploring weight or muscle mass loss often targeted one single factor without controlling for other determinants. Evidence from multifactor studies that consider both lifestyle factors and health conditions is needed.

1.4 BMI and cardiometabolic disease

Diabetes is characterized by high blood glucose levels and insulin resistance, whereas CVDs—including heart diseases and stroke—are mainly caused by narrowed or blocked arteries reducing and preventing blood from flowing to the heart or brain. Diabetes and CVDs share potential pathophysiological mechanisms (e.g., chronic low-grade systemic inflammation) and together are defined as cardiometabolic diseases (CMDs) (45). CMDs are one of the leading causes of morbidity and mortality globally (46). The World Health Organization (WHO) has emphasized the importance of reducing the effects of these diseases (47). Moreover, with improved health services and effective treatment for chronic diseases, many individuals will live for many years with a chronic disease, thus increasing the probability of developing other co-morbid conditions. Cardiometabolic multimorbidity—the coexistence of diabetes, heart disease, or stroke—has been associated with a higher risk for adverse outcomes and substantially reduced life expectancy compared to the presence of a single one of these diseases (48,49).

Overweight and obesity are now the leading cause of the global health burden of CMDs (50,51). A body of prospective studies has found a higher risk of individual CMDs with overweight/obesity in the general population (52–54). However, limited studies have investigated the contribution of overweight/obesity to cardiometabolic multimorbidity (55–57), though the co-occurrence of CMDs has become increasingly common with extended life expectancy. Moreover, poor cardiometabolic risk profiles (e.g., carotid intima-media thickness) due to excess weight may persist even after subsequent weight reduction (18). Estimating the impact of long-term BMI patterns on the risk of CMDs may enhance understanding of the associations between BMI across adulthood and CMDs.

Increasing evidence has documented that both BMI and CMDs are influenced by familial factors (e.g., genetic background and early-life environment) (58–61). Estimates of heritability range from 25% to 70% for BMI (58), from 46% to 90% for diabetes (59), and from 40% to 60% for CVDs (60). Moreover, BMI-related genetic loci overlap with genes implicated in cardiometabolic traits (62). Prior studies have also highlighted the role of early-life environment (e.g., malnutrition during the fetal period and socioeconomic status during childhood) in the development of overweight/obesity and CMDs in adulthood (61,63). However, the role of those familial factors in the BMI-CMD association is still poorly understood. A twin study design provides the possibility to explore whether the BMI-CMD association is independent of shared familial backgrounds. Twins are generally reared together and share a common genetic backgrounds (i.e., 100% for monozygotic twins and 50% for dizygotic twins) (64). Thus, if familial factors play a role in the BMI-CMD association, this association should be attenuated or completely absent among twin pairs relative to the association at the individual level (65).

Role of healthy lifestyle. Due to their effectiveness and safety, lifestyle modifications have long been the cornerstone of weight management (66–68). Increasing evidence has shown that achieving and maintaining a healthy lifestyle, such as engaging in regular physical activity, can help to attenuate the risk of individual CMDs among those with overweight or obesity. An RCT (Da Qing impaired glucose tolerance and Diabetes Study) has reported that physical activity lowered the risk of diabetes among overweight/obese individuals by about 35% (69). In the Diabetes Prevention Program, an intensive lifestyle intervention lowered the risk of diabetes by 58% than placebo group among individuals with overweight and impaired glucose tolerance (70). The lifestyle intervention's benefit for reducing diabetes or CVD risk still persisted over a long post-intervention period (71,72). A recent study demonstrated that overweight/obese individuals who participated in physical activity had around 50% lower 10-year CVD risk than those who were sedentary (73). However, previous RCTs were usually conducted among specific populations, like individuals with impaired glucose tolerance (74), which limits the generalizability of the findings. In addition, studies have reported that other healthy lifestyle behaviors, such as abstention from smoking (75,76) and limited or moderate alcohol consumption (77,78), are also associated with decreased risk of individual CMDs. Because healthy lifestyle behaviors tend to cluster together, it may be more realistic to consider the combinations of different healthy lifestyles when clarifying the role of lifestyles in the BMI-CMDs associations.

1.5 BMI and dementia

There are over 55 million people with dementia in the world, and this number is projected to rise to 78 million by 2030 (79). For individuals aged 75 years and older, dementia is one of the leading causes of disability-adjusted life years (i.e., years of life lost to poor health) (46). Recent studies have reported a decrease in age-specific incidence rates of dementia in the population born more recently, especially in many high-income countries such as the United States and the United Kingdom (80,81), probably due to the improvements in education, socioeconomics, health care, and lifestyle. However, the increasing prevalence of obesity might reverse this trajectory (82,83).

There is consistent evidence that obesity in midlife is a risk factor for dementia, conferring 33% higher risk of dementia compared to normal BMI (83). In the 2020 Lancet Commission on dementia prevention, intervention, and care, midlife obesity was acknowledged as a potentially modifiable risk factor for preventing or delaying dementia (84). However, the association between late-life BMI and dementia is controversial. Most studies have reported that being underweight is related to a higher risk of dementia, while having overweight or obesity is not significantly associated with dementia, or is even associated with lower dementia risk (85,86). Only two studies have reported a positive association between high BMI (as a continuous variable) or obesity and dementia in late life (87,88). The reasons for this discordance in findings between midlife and late life and mixed results among late life are unclear. One explanation is reverse causation: dementia is characterized by a long preclinical phase (up to 20 years) and low BMI may result from underlying dementia (7). Extending the follow-up time and excluding dementia cases that occurred early in follow-up can help account for this bias. However, the longer follow-up capturing the preclinical stage of dementia is costly and usually produces more dropped-out cases, especially in the older population.

Changes in BMI, rather than a single BMI measurement, may be a more informative measure for predicting of dementia risk among older adults. Understanding the role of BMI change in the development of dementia may provide new insights into identifying high-risk populations and shaping possible interventions for preventing or delaying the onset of dementia. Previous studies have consistently shown an association between weight loss and increased dementia risk (89–91). However, the impact of weight gain during the late life on dementia is inconclusive, with different studies relating weight gain to an increase (92–94), decrease (95), or no significant difference (89,90,94,96–98) in dementia risk. Weight gain among older adults primarily represents an increase in fat mass. From the perspective of biological mechanisms, excessive adipose tissue may lead to subsequent dementia in older adults via increasing the concentration of inflammatory markers, promoting neurodegenerative changes (e.g., adipokines regulate neuroinflammation and oxidative stress), and increasing vascular risk. The discrepancies in previous studies may be partly due to methodological differences (e.g., the small sample size of the weight gain group and the short follow-up time without covering the period from weight gain to the development of vascular disorders to the onset of dementia). Moreover, the associations between weight change and dementia were inappropriately assumed to be linear in some studies, which may also distort the estimates.

Role of Apolipoprotein E (*APOE*). The *APOE* ε4 allele is a well-established genetic risk factor for Alzheimer's disease (99,100). The frequency of *APOE* ε4 is higher in Sweden

compared to other European countries (101); around 28% of Swedish older adults have at least one copy of the allele (102,103). Moreover, *APOE* ε4 may exacerbate the impact of obesity on cognitive function (104). *APOE* genotype has also been linked to varied BMI trajectories in old age and *APOE* ε4 carriers showed a faster and earlier decline in BMI (105). However, whether *APOE* ε4 allele can exacerbate the dementia risk associated with weight change remains unclear.

1.6 BMI and survival

Several studies have investigated the associations between late-life high BMI and mortality, with inconsistent results (14,106–114). Most studies have reported that being overweight in old age is associated with lower mortality risk (106–109,114) or no significant difference in mortality risk compared to being normal weight in old age (111). Obesity, especially morbid obesity (≥40 kg/m^2), has been associated with higher mortality (110,111,115), though some studies have reported a neutral (108,109,112) or negative (113,116) association. In a meta-analysis of 239 prospective studies of chronic disease-free never-smokers, the nadir of the BMI-mortality association curve was 22 kg/m^2 for those aged 35 to 49 years and 24 kg/m^2 for those aged 70 to 89 years, both of which were within the WHO's recommended normal BMI range (10). However, a recent meta-analysis including participants aged ≥65 years identified a BMI of 27 to 28 kg/m^2 (classified as overweight) as having the lowest risk of mortality, and the result did not change largely when analyses were restricted to never-smokers (9). Moreover, being overweight among older adults with chronic diseases seemed to be associated with lower mortality (117–119). Obesity has also been associated with lower mortality among people with CVDs (118), diabetes (119,120), and cancer (121). Those contradictory findings have made it difficult to develop recommendations for weight management among older adults.

Disease-free survival. Prolonged life expectancy without a proportional increase in years lived in good health may result in reduced quality of life and lead to a heavy burden for society and the healthcare system. Thus, metrics like disease-free survival, which account for both lifespan and healthy survival, may provide more information for health professionals and policymakers when evaluating the health consequences of high BMI. Previous studies quantifying disease-free survival in relation to overweight/obesity mainly focused on survival free from specific chronic diseases, such as CVD or diabetes, and have reported mixed findings (54,122–127). Some studies have reported that overweight and obesity are associated with shorter healthy survival (124–126). In contrast, others found that being overweight was associated with a similar duration of chronic disease-free survival compared to having a normal BMI (54,127). Older adults – particularly those with high BMI – are more likely to be affected by multiple chronic diseases. Previous studies have defined disease-free survival using several major obesity-related chronic diseases (125,126,128), however, more evidence is needed to comprehensively assess the loss of disease-free years attributed to high BMI in older adults. Moreover, the influence of BMI change on health may vary over the life course (129). It remains unclear how the timing of the development of overweight/obesity over the life course and the transitions between BMI categories from mid to late life may impact chronic disease-free survival.

1.7 Knowledge gaps

First, the changes in body composition that occur with age need to be further characterized. Although previous studies have assessed changes in directly measured fat mass and muscle mass, very few studies have explored the trajectories of simple, easy-to-measure anthropometric measures (i.e., BMI, CC, and MAC), which are more practical for monitoring long-term changes. Understanding the determinants of these changes is important for identifying high-risk populations and further providing prevention.

Second, the impact of high BMI on CMDs needs to be further verified, especially in relation to cardiometabolic multimorbidity, which is increasingly becoming a public health challenge with global population aging. In particular, questions remain regarding the extent to which familial factors (i.e., genetic background and early-life environment) influence the association between high BMI and CMDs as well as whether healthy lifestyles can compensate for the risk of CMDs among people who are overweight or obese.

Third, previous findings on an association between BMI change, especially BMI gain, in late life and dementia risk are mixed. This is likely because of methodological issues (e.g., the small sample size of the BMI gain group and the assumed linear association between BMI change and dementia). Therefore, evidence from large-scale cohort studies with a long follow-up are needed to clarify the dementia risk associated with large BMI loss or gain. Additionally, the *APOE* ε4 allele is a well-known genetic risk factor for Alzheimer's disease-related dementia (99,100). However, the role of the *APOE* ε4 allele in the association between BMI change and dementia risk has not yet been explored.

Finally, it is important to understand the relationship between BMI and overall and disease-free survival, considering the spectrum from disease-free states to the development of multiple chronic diseases and finally mortality. Exploring the associations between mid and late-life BMI profiles and overall and disease-free survival will contribute to planning preventions over the lifespan to expand the length of disease-free survival.

1.8 Hypothesis

The projects in this thesis are based on the hypothesis that, on one hand, BMI may decline with advancing age, likely because of progressive loss of muscle mass. At the same time, BMI can also increase—likely reflecting a gain in fat mass—and this increase in BMI could be associated with increased risk of dementia risk. Additionally, high BMI in mid- or late-life might also increase the risk of CMDs and shorten chronic disease-free survival in older adults.

2 AIMS

The overarching goal of this thesis is to assess the trajectories of anthropometric measures in older age and examine the association of BMI and BMI changes with cardiometabolic diseases, dementia, and survival. To achieve this, four individual studies were carried out addressing the specific aims below:

Study I aimed to explore the trajectories of BMI, CC, and MAC over 15 years in older adults and to assess the influence of sociodemographic factors, lifestyle factors, vascular disorders, and diabetes on these trajectories.

Study II aimed to examine the associations between BMI and individual CMDs as well as cardiometabolic multimorbidity, to explore whether these associations are independent of familial factors and whether a favorable lifestyle can attenuate the risk of CMDs among participants with overweight or obesity.

Study III aimed to investigate the relationship between BMI change and dementia risk in late life, and to explore the role of *APOE* genotype in this association.

Study IV aimed to assess the associations of late-life BMI and BMI change over mid-to-late life with survival free from chronic diseases (i.e., diabetes, heart disease, stroke, and cancer).

3 MATERIALS AND METHODS

3.1 The Swedish National study on Aging and Care-Kungsholmen (SNAC-K)

3.1.1 Study population

The SNAC-K is an ongoing population-based cohort study consisting of individuals aged ≥60 years and living at home or institutions in Kungsholmen - the central area of Stockholm, Sweden. Stratified sampling was used; the Kungsholmen population was stratified by age and then a random sample was selected from each age group. There were 11 age cohorts, including the younger cohorts with 6-year intervals (60, 66, and 72 years) and the older cohorts with 3-year intervals (78, 81, 84, 87, 90, 93, 96, and ≥99 years). Of the 5,111 persons selected to participate, 262 had no contact information, 200 died before the start of the study, and 59 were non-Swedish speakers, deaf, or moved away. Of the remaining 4,590 alive and eligible adults, 3,363 participated in the baseline assessment (response rate 73.3%) from March 2001 through June 2004. Follow-up assessments were conducted every three years for the older cohorts and every six years for the younger cohorts (**Figure 1**).

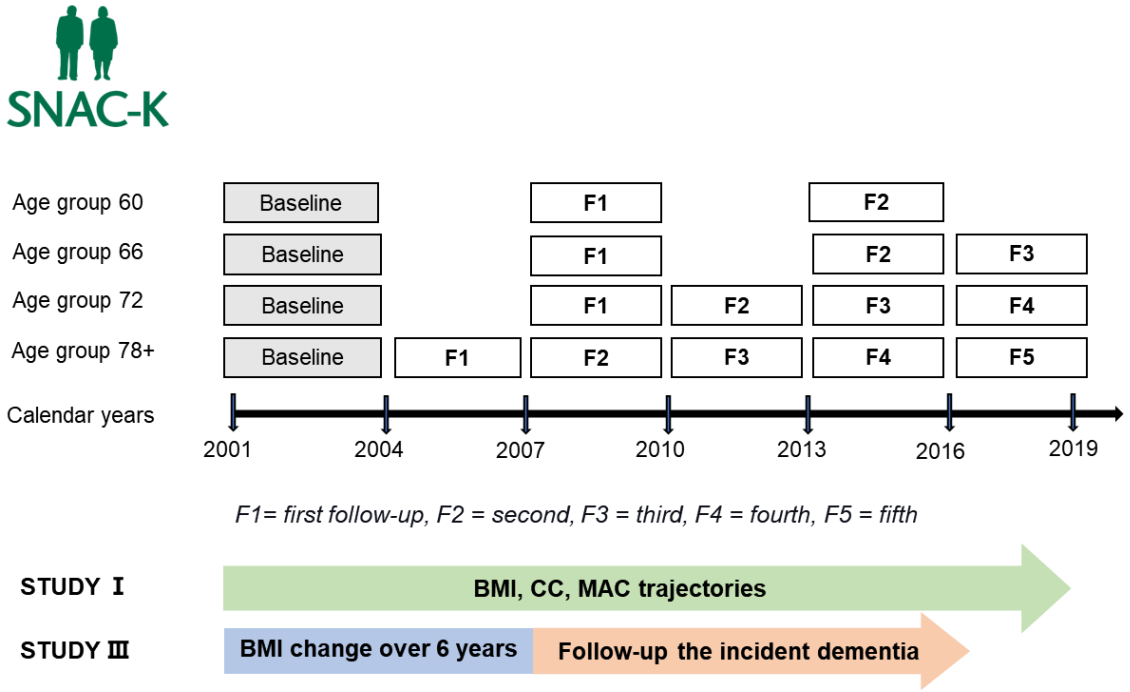

Figure 1. Timeline of data collection in SNAC-K.

SNAC-K data were used for *Studies I & III*. Participants were included in *Study I* if they 1) were dementia-free at baseline and 2) had at least two repeated BMI, CC, and MAC measurements. A total of 2,155 participants were included in the analysis. Participants were included in *Study III* if they 1) had BMI measurements at baseline and at the 6-year follow-up

assessment (i.e., having the BMI change information), 2) were dementia-free during the first 6-years of follow-up, and 3) participated in second 6-year follow-up. A total of 1,673 participants were included as the analytical sample.

3.1.2 Data collection

Data collection at baseline and each follow-up assessment were conducted according to a standard protocol (available at https://www.snac-k.se/). Each participant was examined for about six hours during the baseline assessment and about four hours during each follow-up assessment. Information about sociodemographic factors and lifestyle factors was collected by trained nurses. Trained physicians collected medical history and medication use and conducted clinical examinations. Trained psychologists performed a comprehensive neuropsychological testing battery. Peripheral blood samples were taken from all participants for laboratory testing. Medical conditions in the SNAC-K were additionally captured via the Swedish National Patient Register (NPR) using the International Classification of Diseases (ICD) codes, 10th edition, and information on death was derived from the Swedish Cause of Death Register.

3.1.3 Assessment of BMI

Trained nurses measured the weight and height of participants wearing light clothes and no shoes at baseline and each follow-up assessment. Self-reported measurements were used if there was no measured weight or height. BMI (kg/m^2) was calculated using weight in kilograms divided by height in meters squared and categorized into four groups: underweight (<20 kg/m^2), normal weight (20–25 kg/m^2), overweight (25–30 kg/m^2), and obesity (≥30 kg/m^2) (130). Percent change in BMI and absolute weight change over 6 years were calculated as follows.

$$\text{Percent change in BMI (\%)} = (\text{BMI}_{\text{at first 6-year follow-up}} - \text{BMI}_{\text{at baseline}})/\text{BMI}_{\text{at baseline}}$$

$$\text{Weight change (kg)} = \text{weight}_{\text{at first 6-year follow-up}} - \text{weight}_{\text{at baseline}}$$

BMI change was categorized into the following groups: large loss (>10%), moderate loss (5–10%), stable (≤5%), moderate gain (5–10%), and large gain (>10%) (94). Weight change was categorized into the following groups: large loss (>7.5 kg), moderate loss (2.5–7.5 kg), stable (≤2.5 kg), moderate gain (2.5–7.5 kg), and large gain (>7.5 kg). BMI change and weight change were analyzed separately.

3.1.4 Assessment of mid-arm circumference and calf circumference

MAC was measured at the mid-point between the tip of acromion process and the tip of the olecranon process, with the elbow bent at a 90° angle (131). CC was measured at the point of maximum convexity of the calf with the participants sitting down so that the knee and ankle

were each bent at a 90° angle (131). Both were measured on the right side of the body and rounded to 1 centimetre (cm).

3.1.5 Assessment of other factors

Sociodemographic factors. Age was dichotomized into younger-old (<78 years) vs. older-old cohort (≥78 years). Educational attainment was categorized as elementary, professional school, high school, and university.

Lifestyle factors. Smoking status was recorded as never, former, or current smoker. Alcohol consumption was classified as never, occasional, light-to-moderate (1–14 drinks per week for men or 1–7 drinks per week for women), or heavy (>14 drinks per week for men or >7 drinks per week for women) drinking (132). Physical activity was assessed based on the frequency and intensity of physical exercise patterns during the last 12 months and was categorized as inactive (≤2–3 times/month of light-to-intense exercise), moderate (several times per week or everyday of light exercise: walking along roads or in parks, walking in the woods, short bicycle rides, light aerobics, golf), or vigorous (several times per week or every day of moderate-to-intense exercise: jogging, long power walks, heavy-duty gardening, long bicycle rides, high-intensity aerobics, long distance ice skating, swimming, ball sports [not golf] or other similar activity) (133). Physical activity was also dichotomized into inactive and active (i.e., moderate or vigorous).

Medical conditions. Hypertension was identified based on measured systolic and diastolic blood pressure ≥140/90 mmHg, medical records in the NPR (ICD-10 codes: I10-13 and I15), or self-reported use of antihypertensive treatment. Type 2 diabetes was identified based on self-reported medical history, glucose-lowering medication use, records in the NPR (E11), or glycated hemoglobin (HbA1c) ≥6.5% (134). Ischemic heart disease (I20–22, I24–25, Z951 and Z955), heart failure (I110, I130, I132, I27, I280, I42–43, I50, I515, I517, I528, Z941 and Z943), and cerebrovascular disease (G45–46, I60–64, I67 and I69) were identified from records in the NPR or diagnosed during the clinical examinations performed by physicians.

Global cognitive function. The Mini-Mental State Examination (MMSE) was administered to assess global cognitive function at baseline and each follow-up assessment (135), with a maximum score of 30 points.

Genetic factor. *APOE* genotypes were assessed using a microsequencing method (AffiGen *APOE*, Sangtec Medical) from blood samples and dichotomized into ε4 carriers and non-carriers.

3.1.6 Diagnosis of dementia

Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) criteria using a validated three-step procedure (136). Preliminary diagnoses were made independently by two physicians based on the participant's physical, neurological, and cognitive status (steps one and two). In case of disagreement between these two diagnoses, a deciding diagnosis was sought by a neurologist external to the data collection

(step three) (137). Standard criteria were used to diagnose Alzheimer's disease and vascular dementia (138,139). For participants who died during follow-up without a prior dementia diagnosis, dementia status was verified through death certificates from the Swedish Cause of Death Register and clinical charts via linkage to medical records at hospital discharge when available.

3.2 The Screening Across the Lifespan Twin study (SALT)

3.2.1 Study population

The SALT study was conducted from March 1998 to December 2002 with the aim of screening all living twins in the Swedish Twin Registry (STR, initiated in the 1950s) born in 1958 or earlier. A computer-assisted telephone interview was performed to collect information at baseline. Efforts were made to interview co-twins within a twin pair within a month of one another to minimize the bias resulting from differential age effects. A total of 44,919 twin individuals aged between 41 and 103 years completed the telephone interview (response rate: 74%). Moreover, BMI was self-reported via questionnaires distributed in 1963, 1967, 1970, or 1973 (i.e., 25 to 35 years before baseline) for twin individuals included in SALT (**Figure 2**).

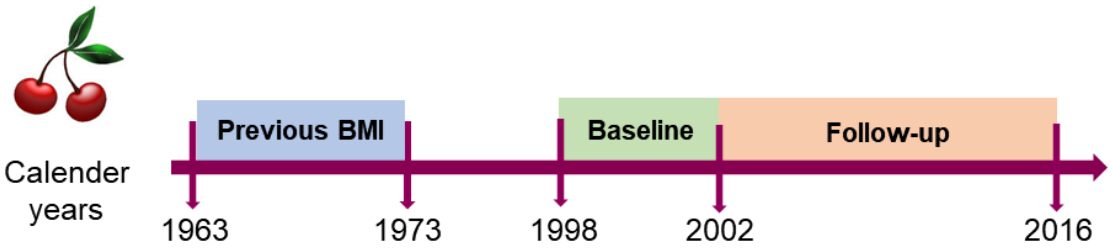

Figure 2. Timeline of data collection in SALT.

SALT data were used for *Studies II & IV*. **Figure 3** shows the flow chart of the study population in *Study II*. A total of 36,622 participants aged >40 years were included in the analyses for the associations between BMI and individual CMDs or cardiometabolic multimorbidity. We included 729 BMI- and CMD-discordant twin pairs in the co-twin analysis to explore whether the BMI-CMD association was independent of shared familial backgrounds. Moreover, we included 20,606 participants with self-reported BMI 25 to 35 years before the baseline in the analysis for the association between long-term BMI changes and CMD risk.

Participants were included in *Study IV* if they 1) were diabetes-, CVD-, and cancer-free at baseline and 2) had data on self-reported BMI at baseline. In total, we included 11,597 participants aged 60 to 79 in the analysis of late-life BMI and survival. We later excluded those without self-reported BMI 25 to 35 years before baseline, leaving 6,686 participants for the analysis of mid-to-late life BMI and survival (**Figure 3**).

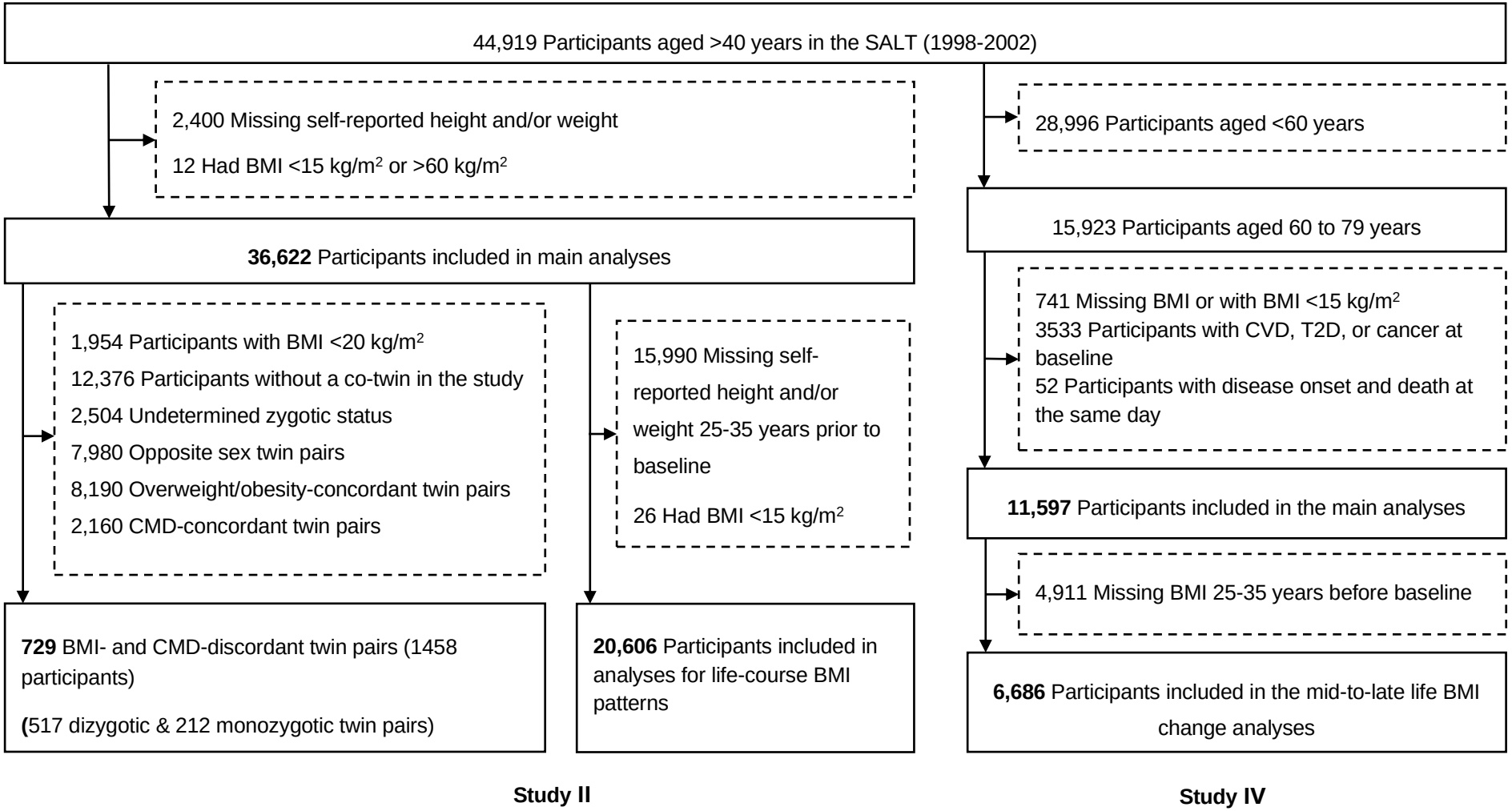

Figure 3. Flow chart of SALT population in Study II and IV.

3.2.2 Data collection

At baseline, information on sociodemographic factors, lifestyle factors, and zygosity was self-reported. Diagnoses of medical conditions were collected from the Swedish health registers using ICD codes (ICD-7 was used from 1964 to 1968; ICD-8 was used from 1969 to 1986; ICD-9 was used from 1987 to 1996; ICD-10 was used from 1997 and onward). Prescriptions for antidiabetic drugs were captured from the Swedish Prescribed Drug Register beginning in 2005. Death information was collected from the Swedish Cause of Death Register.

3.2.3 Assessment of BMI

Weight and height were self-reported during the telephone interview. BMI (kg/m^2) was calculated as weight in kilograms divided by height in meters squared. Besides baseline BMI, information on BMI 25 to 35 years before the baseline was collected in the STR by the self-reported questionnaires sent out in 1963, 1967, or 1970 for twins born between 1886 and 1925, and in 1973 for twins born between 1926 and 1958 (64). BMI was categorized into four groups: underweight (<20 kg/m^2), normal weight (20–25 kg/m^2), overweight (25–30 kg/m^2), and obesity (≥30 kg/m^2) (130). Overweight and obesity were further grouped as overweight/obesity (i.e., high BMI, ≥25 kg/m^2) for data analysis. BMI change from earlier (i.e., 25 to 35 years before baseline) to later life (i.e., the baseline of SALT) was categorized into the following groups: 1) underweight to underweight, 2) underweight to normal BMI, 3) stable normal BMI, 4) normal BMI to underweight, 5) overweight/obesity only in earlier life, 6) overweight/obesity only in later life, 7) overweight/obesity both in earlier and later life. The latter three groups were also combined as overweight/obesity in earlier or/and later life. The reference group was participants with stable normal BMI.

3.2.4 Ascertainment of CMDs, cancer, and death

CMDs include diabetes, heart disease, and cerebrovascular disease. Diabetes was derived from the NPR (ICD-7 code 260, ICD-8 and -9 code 250, and ICD-10 codes E11-E14) and the Swedish Prescribed Drug Register (ATC A10). CVDs, including heart disease (ICD-7 codes 420, 433, and 434, ICD-8 and -9 codes 410-414, 427, and 428, ICD-10 codes I20-I25, I48-I50) and cerebrovascular disease (ICD-7 codes 330-334, ICD-8 codes 430-438, ICD-9 codes 430-437, ICD-10 codes I60-I68), were derived from the NPR and the Swedish Cause of Death Register. Incident CMD was defined as the occurrence of diabetes or/and CVDs. Cardiometabolic multimorbidity was defined as having at least two of the following: diabetes, heart disease, and cerebrovascular disease. In *Study II*, diagnoses of incident CMDs were identified from baseline (1998 to 2002) to December 31, 2014. In *Study IV*, diagnoses of incident CMDs were identified from baseline to December 31, 2016.

Cancer diagnoses were derived from the NPR and the Swedish Cancer Register (ICD-7 codes 140-205, except 191 for nonmelanoma skin cancer; ICD-8 codes 140-209, except 173 for nonmelanoma skin cancer; ICD-9 codes 140-208, except 173 for nonmelanoma skin cancer; ICD-10 codes C00-C97, except C44 for nonmelanoma skin cancer). The age at cancer onset

was estimated as the earliest date of cancer diagnosis recorded in the NPR or the Swedish Cancer Register.

Information on death and cause of death were obtained through linkage to the Swedish Cause of Death Register.

3.2.5 Assessment of other factors

Sociodemographic factors. Education was dichotomized as <8 years vs. ≥8 years based on the maximum years of formal schooling attained. Marital status was dichotomized as married/cohabitating vs. single.

Lifestyle factors. Smoking history was categorized as never vs. former/current smoker. Alcohol consumption was dichotomized as no/mild vs. heavy drinking. Physical activity during the last 12 months was dichotomized as low vs. regular physical activity. A favorable lifestyle was defined as having two or three of healthy lifestyle factors, i.e., not smoking, having no or only mild alcohol consumption, and regular physical activity.

Medical conditions. Hypertension and dyslipidemia were self-reported by participants during the baseline telephone interview.

3.3 Statistical analysis

In general, baseline characteristics of participants across groups were compared using the *Chi-square* test for categorical variables and *t*-tests (for two groups) or one-way analysis of variance (ANOVA) (for more than two groups) for continuous variables. Bonferroni correction was used to minimize the type I error from multiple comparisons and multiple tests. Specific analytical methods, including linear mixed-effect models, Cox proportional hazards models, stratified Cox proportional models, and multistate models, were used in each study. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and R software. Statistical significance was defined as two-sided *P*-value <0.05. Both point estimates and 95% confidence intervals (CIs) were reported. **Table 1** shows a summary of the statistical methods used in each study.

3.3.1 Linear mixed effect model

In longitudinal datasets, repeated measurements from a single individual will typically be correlated/non-independent of one another. The distinct feature of the mixed-effect model is that it contains both fixed and random effects, accounting for not only between-subject but also within-subject variability. Moreover, mixed-effect models can accommodate unbalanced longitudinal data, such as different number of repeated measurements for each participant.

In *Study I*, we first tested whether trajectories of BMI, CC, or MAC were non-linear over time by introducing an additional quadratic term for follow-up time in the model. We performed linear mixed-effect models to calculate the annual rate of change in BMI, CC, and

MAC because the quadratic term of time was not statistically significant. Random effects included a random intercept and a random slope of follow-up time for each participant, assuming an unstructured covariance structure. To explore the differences in annual rate of change in these measurements across baseline sociodemographic, lifestyle, and health conditions, we simultaneously included these variables, the follow-up time, and their interaction term (each variable × follow-up time) as fixed effects. All analyses were stratified by age cohort: younger-old (<78 years) and older-old (≥78 years).

3.3.2 Cox proportional hazards model

The Cox proportional hazards model is a semi-parametric model because there are no assumptions about the shape of the baseline hazard function. The proportional hazard assumption was tested in our studies (*Study II, III, and IV*) using Schoenfeld residuals or by using time-dependent explanatory variables (e.g., including the interaction term of variable and log(time)), and no violations of proportionality were detected.

In *Study II*, we applied Cox proportional hazards models to estimate the associations of BMI and life-course BMI patterns with CMDs. Robust sandwich estimators were used to correct the standard errors in order to account for the clustering of twins within a pair. Follow-up time, as the time scale, was calculated as the time from baseline until the onset of CMDs, death, or the end of follow-up (December 31, 2014), whichever occurred first. In the multi-adjusted model, we included baseline age, sex, education, marital status, smoking status, alcohol consumption, physical activity, and prevalent hypertension. To explore whether a healthy lifestyle can counteract the increased CMD risk associated with overweight and obesity, we combined BMI status (overweight/obesity and normal) and lifestyle status (unfavorable and favorable) and examined their joint effect on CMD risk. Moreover, both multiplicative and additive interactions between BMI status and lifestyles were calculated by introducing their cross-product term in the model. The relative excess risk due to interaction (RERI) was calculated as the joint excess relative risk for both exposures (overweight/obese and unfavorable lifestyle: HR_{11} - 1) minus the excess relative risk for overweight/obese (HR_{10} - 1), and excess relative risk for unfavorable (HR_{01} - 1). The 95% CIs were calculated using an Excel spreadsheet provided by Tyler J. Vanderweele (140).

The twin study design provided an opportunity to explore whether the BMI-CMD associations independent of shared familial background (i.e., genetic background and early-life environmental factors). We conducted a stratified Cox proportional hazards model among twin pairs discordant for BMI categories and for CMD status (with or without incident CMD or with different CMD onset dates). If the BMI-CMD association attenuated within twin pairs, it indicates that familial factors may confound the BMI-CMD association. An interaction term between BMI groups and zygosity was introduced to the model to explore whether BMI-CMDs associations varied as a function of zygosity (141). A significant interaction indicates that genetic background may play a role in the associations.

In *Study III*, we used Cox proportional hazards models to explore the associations between BMI change (both as a continuous and a categorical variable) over six years and subsequent dementia. Follow-up time was calculated from the 6-year follow-up until dementia diagnosis,

death, or the last follow-up assessment, whichever occurred first. The HR for dementia in relation to continuous BMI change was modeled using restricted cubic splines. It uses a set of cubic polynomials to represent the non-linear association between the continuous variable and outcome. We selected four knots at the 5th, 35th, 65th, and 95th percentile of BMI (142). The multi-adjusted model included age, sex, education, smoking status, alcohol consumption, physical activity, hypertension, CVDs, diabetes, depression, and *APOE* ε4 carrier status.

In *Study IV*, we performed Cox models to examine the associations of late-life BMI and mid-to-late-life BMI patterns with the combined outcome, i.e., incident chronic disease or death. Follow-up time was calculated from baseline (1998-2002) until the onset of any chronic diseases, death, or end of follow-up (December 31, 2016), whichever occurred first. Models were adjusted for age, sex, education, marital status, smoking status, alcohol consumption, physical activity, hypertension, and dyslipidemia.

3.3.3 Multi-state model

In *Study IV*, the multi-state Markov model was used to estimate the transitions between different health states. The underlying assumption of the multi-state Markov model is that the probability distribution of future states depends only on the current state but not the past state. **Figure 4** provides a schematic representation on the multi-state model in our study. This is a nonrecoverable disease-death model, in which there are three possible states—chronic disease-free, chronic diseases, and death—and three possible transitions—from chronic disease-free to chronic disease, form chronic disease-free to death, and from chronic disease to death. The probability of transiting from one state to another has been derived using age as the time scale and the Gompertz distribution to fit the transition hazard (143).

The exposures (i.e., late-life BMI categories or mid-to-late life BMI patterns) and the baseline covariates were adjusted for all three transitions. Based on the parameters derived from the multi-state Markov model, we used the R package named *Estimating Life Expectancies using Continuous Time (ELECT)* to estimate the overall survival and chronic disease-free survival (i.e., free from diabetes, CVDs, or cancer) at age 60 in relation to the exposures.

All multi-state Markov models were adjusted for age, sex, education, marital status, smoking status, alcohol consumption, physical activity, hypertension, and dyslipidemia. All analyses were conducted separately among the overall population and men and women.

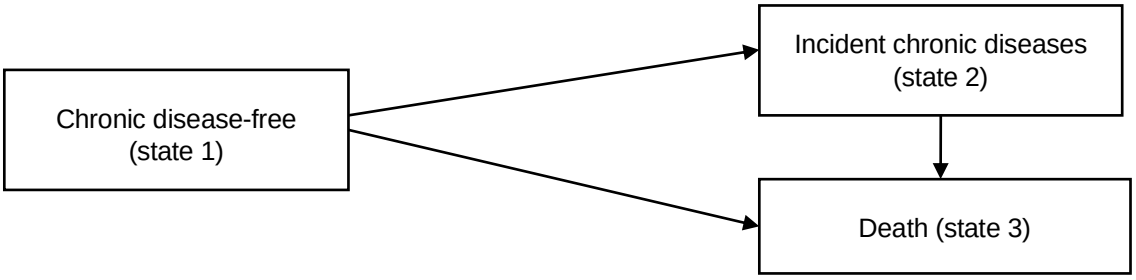

Figure 4. Multistate model in Study Ⅳ.

Table 1. Overview of the studies and main methods included in this thesis.

Study	Title	Exposures	Outcomes and follow-up time	Potential confounders	Statistical analyses
Study Ⅰ	Individual changes in anthropometric measures after age 60 years: a 15-year longitudinal population-based study	Age, sex, education, smoking status, alcohol consumption, physical activity, vascular disorders, diabetes	Annual changes in BMI, CC, and MAC during 15-year follow-up	Mutually adjusted for each other	Linear mixed effect model
Study Ⅱ	Association of body mass index and its long-term changes with cardiometabolic diseases: A nationwide twin study	BMI, combinations of BMI status at baseline and 25 to 35 years before baseline	Incident CMDs or cardiometabolic multimorbidity during 16-year follow-up	Age, sex, education, marital status, smoking status, alcohol consumption, physical activity, hypertension	Cox regression model, stratified Cox regression model for co-twin analyses
Study Ⅲ	Association between late-life weight change and dementia: A population-based cohort study	BMI change over 6 years	Incident dementia during 6-year follow up	Age, sex, education, smoking status, alcohol consumption, physical activity, hypertension, CVDs, diabetes, depression, and *APOE* ε4 carrier status	Cox regression model, restricted spline curve to estimate the risk of continuous BMI
Study Ⅳ	Associations between mid-to-late life body mass index and chronic disease-free survival: A nationwide twin study	BMI, combinations of BMI status at baseline and 25 to 35 years before baseline	A composite outcome of chronic diseases (i.e., diabetes, CVD, and cancer) or death during 18-year follow up; chronic disease-free survival at age 60	Age, sex, education, marital status, smoking status, alcohol consumption, physical activity, hypertension, dyslipidemia	Cox regression model, multi-state model

BMI, body mass index; CC, calf circumference; MAC, mid-arm circumference; CMD, cardiometabolic disease; CVD, cardiovascular disease; *APOE* ε4, apolipoprotein ε4 allele.

3.4 Ethical considerations

Both SNAC-K and SALT received ethical permission from the Ethics Committee at Karolinska Institutet and the Regional Ethical Review Board in Stockholm. Informed consent (written or oral) was collected from all participants at the beginning of these projects, per the Declaration of Helsinki **(Table 2)**.

Table 2. List of ethical permits for SNAC-K and SALT.

Dataset	Registration numbers and date
SNAC-K	Baseline: 01-114, 2001-06-18
	First follow-up: 04-929/3, 2005-01-19
	Second follow-up: Ö26-2007, 2007-09-20
	Register data: 2009/595-32, 2009-03-30
	Third follow-up: 2010/447-31/2, 2010-06-09
	Fourth follow-up: 2013/828-31/3, 2013-05-29
	Fifth follow-up: 2016/730-31/1, 2016-02-01
SALT	97-051, 1997-02-10; 2016/2263-31/1, 2016-12-14

In SNAC-K, a series of strategies were implemented to minimize discomfort among the subjects. At the beginning of this study, a personal letter was sent to the eligible subjects to explain the study's content, purpose, duration, and the importance of participation, clearly stating that participation was voluntary and that participants could discontinue participation at any time. If a person had cognitive impairment, a proxy (e.g., a close family member) was asked for consent. To verify participants' availability, nurses telephoned those who agreed to participate to schedule the first study visit. Participants were assessed in a friendly and comfortable environment with sufficient time to finish the examination. If the participant expressed discomfort, the interview was terminated. If any new diseases were detected during the medical examination, participants were asked if they wanted to be informed of the results. In such cases, participants were referred to their family doctors or other physicians. Participants could receive written reports of their laboratory test results if requested. As part of the informed consent process, participants were assured that their data would remain confidential and anonymous. All participants were informed about the progression and results of the research through seminars organized by the researchers and in the form of small reports and popular scientific publications.

In SALT, all participants received a letter that described the study's purpose, content, and duration and were assured confidentiality and anonymity as part of the informed consent

process. Participants were informed that their involvement in the study was voluntary and that they were free to drop out at any point in time.

For data collected through the national register system, ethical requirements clearly state that consent must be voluntary. This means that information on the health status of participants who dropped out was not extracted from the registers (with the exception of data on vital status, which is not covered by privacy law). In all datasets, researchers obtained anonymized data without any reference to a person's name or personal identification number; data were tagged with only a study-specific ID number.

4 RESULTS

4.1 Trajectories of anthropometric measures and determinants (Study I)

4.1.1 Population characteristics

The analytical sample included 2,155 dementia-free participants from the SNAC-K with a mean baseline age of 71.3 years (standard deviation [SD]: 9.6 years). Of them, 63.0% were female and 35.5% had a university education.

4.1.2 Trajectories of BMI, CC, and MAC across age groups

Among participants aged 60 years at baseline, BMI remained stable (β [95% CI]: 0.009 [-0.006, 0.024], $P = 0.234$) while CC (-0.033 [-0.051, -0.016]) and MAC (-0.042 [-0.059, -0.024]) significantly declined overtime (**Figure 5**). Among participants aged 66, 72, 78, 81+ years at baseline, all three measures declined significantly ($P < 0.001$). The z-scores of CC and MAC declined faster than that of BMI in the younger-old cohort (<78 years), whereas all three measurements declined parallelly in the older-old cohort (≥78 years) (**Figure 6**).

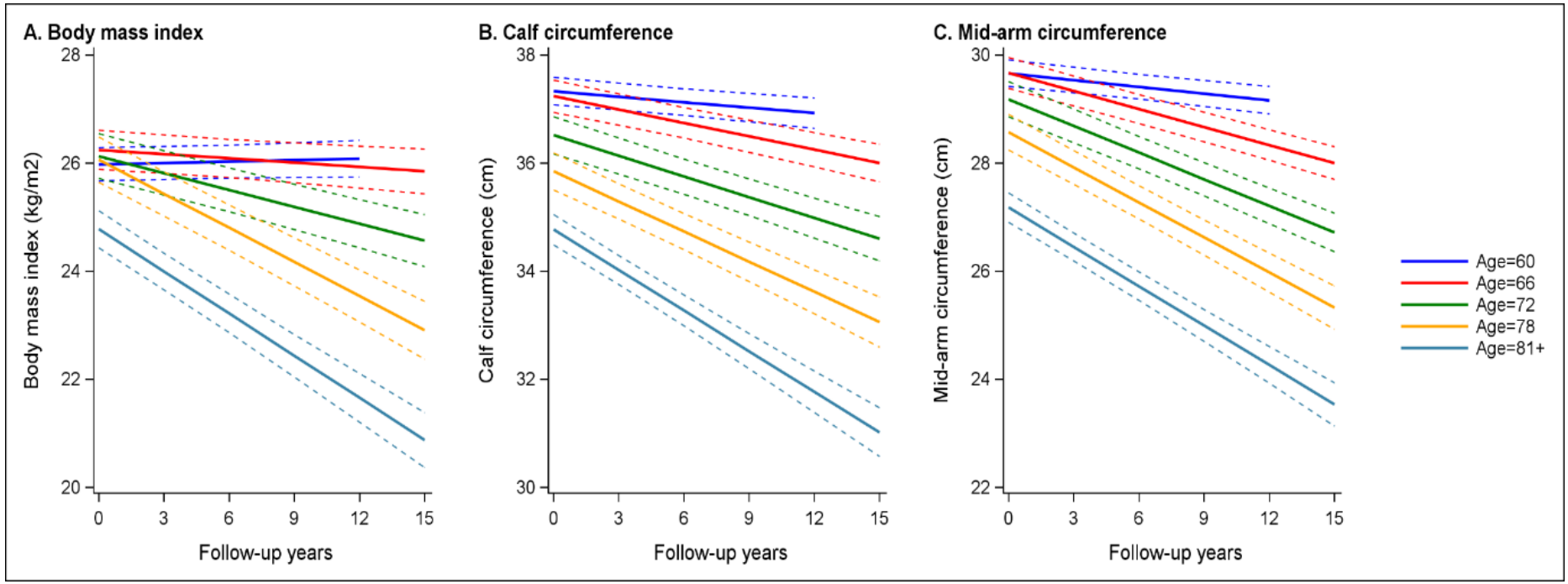

Figure 5. Trajectories of body mass index (BMI), calf circumference (CC), and mid-arm circumference (MAC) during 15-year follow-up across age groups.

Solid lines represent the estimated means of BMI, CC, or MAC over the 15-year follow up and dashed lines represent the 95% confidence interval of estimated means. This figure is produced from Guo et al Age and Ageing 2021 (144).

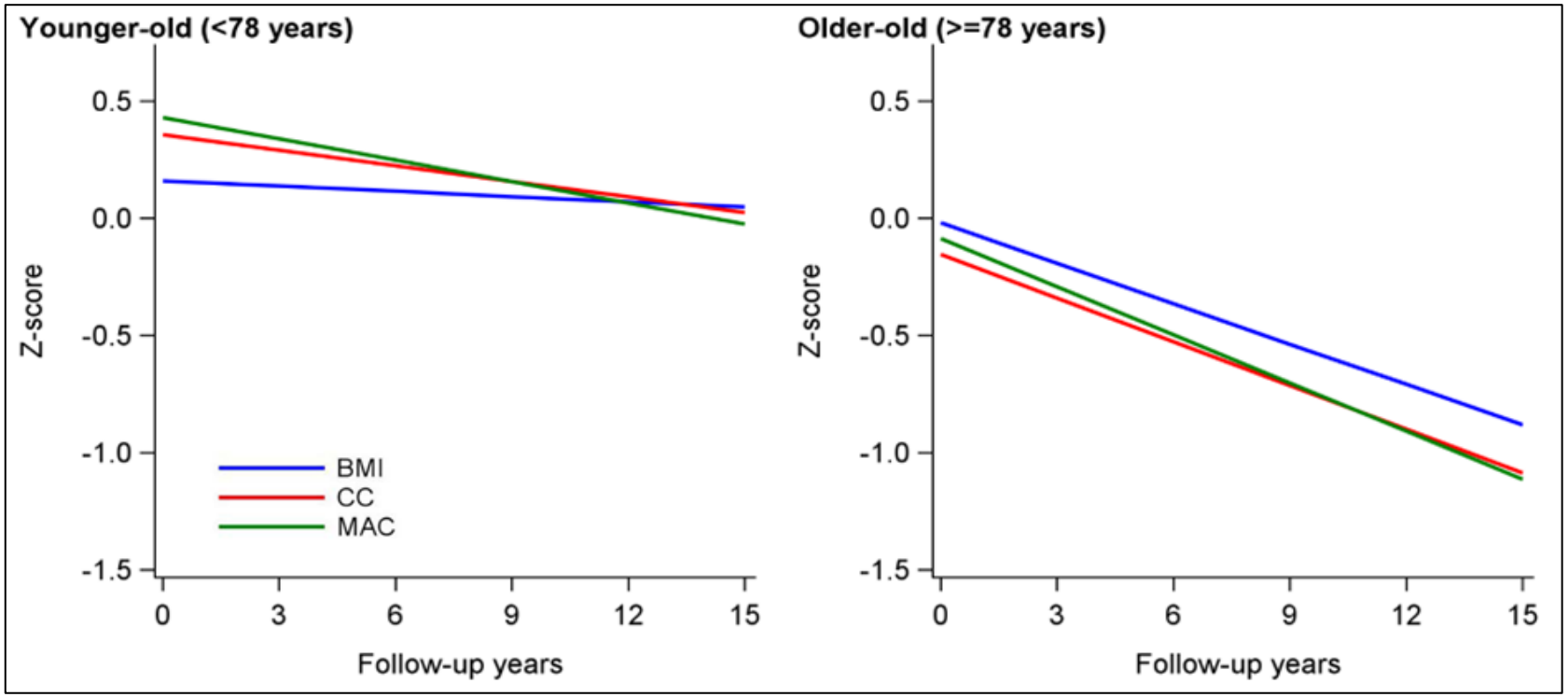

Figure 6. Trajectories of the z-scores of body mass index (BMI), calf circumference (CC), and mid-arm circumference (MAC) over 15 years among younger-old and older-old participants.

All declines were statistically significant (*P* <0.001). This figure is produced from Guo et al Age and Ageing 2021 (144).

4.1.3 Factors related to trajectories in BMI, CC, and MAC across age groups

In the younger-old cohort, more educated participants had slower declines in BMI, CC, and MAC, while those with vascular disorders or diabetes had faster declines in these three measures (P <0.05 for all) (**Table 3**). In the older-old, participants with moderate or vigorous physical activity had slower declines in BMI and CC, whereas those with any vascular disorders had faster declines in BMI and MAC (P <0.05 for all).

Table 3. β_{slope} and 95% CI of the associations of sociodemographic, lifestyle and health conditions with changes in BMI, CC, and MAC over 15 years: results from linear mixed models

Factors	BMI	CC	MAC
	β (95%CI) [a]	**β (95%CI) [a]**	**β (95%CI) [a]**
<78 years			
Education			
Elementary/ professional school	Reference	Reference	Reference
High school	-0.006 (-0.041, 0.030)	0.002 (-0.036, 0.039)	-0.009 (-0.043, 0.026)
University	**0.031 (0.008, 0.054)**	**0.034 (0.009, 0.058)**	**0.029 (0.006, 0.052)**
Vascular disorders [b]			
None	Reference	Reference	Reference
Any	**-0.028 (-0.051, -0.005)**	**-0.035 (-0.060, -0.011)**	**-0.030 (-0.053, -0.008)**
Diabetes			
No	Reference	Reference	Reference
Yes	**-0.118 (-0.163, -0.072)**	**-0.075 (-0.123, -0.026)**	**-0.088 (-0.133, -0.044)**
≥78 years			
Physical activity			
Inactive	Reference	Reference	Reference
Moderate	0.051 (-0.013, 0.116)	**0.088 (0.029, 0.147)**	0.049 (-0.003, 0.100)
Vigorous	**0.087 (0.005, 0.169)**	**0.132 (0.057, 0.207)**	0.044 (-0.021, 0.109)
Vascular disorders [b]			
None	Reference	Reference	Reference
Any	**-0.110 (-0.191, -0.030)**	-0.035 (-0.108, 0.038)	**-0.093 (-0.157, -0.030)**

BMI, body mass index; CC, calf circumference; MAC, mid-arm circumference.
[a] Adjusted for sex, education, smoking status, alcohol consumption, physical activity, vascular disorders, and diabetes and their interaction term with follow up years (factors × follow up time). Only statistically significant results are shown here; full results are presented in the attached article.
[b] Vascular disorders were coded as none, or the presence of any of the following diseases: hypertension, ischemic heart disease, heart failure, or cerebrovascular disease.

4.2 BMI and cardiometabolic disease (Study II)

4.2.1 Population characteristics

A total of 36,622 CMD-free participants aged >40 years from SALT were included. The mean age at baseline was 57.3 (SD: 9.9 years) and 19,952 (54.5%) were female. Participants with overweight or obesity were more likely to be older, less educated, former/current smokers, heavy drinkers, and have hypertension at baseline (P <0.05 for all) compared to those with normal BMI.

4.2.2 Association between high BMI and CMDs

During a median follow-up of 13.5 years (interquartile range: 10.1 to 14.8), 11,202 (30.6%) incident CMDs cases occurred, including 2,885 cases of diabetes and 9,587 cases of CVDs. Over follow-up, 2,586 participants developing more than one CMD (i.e., 1,316 with heart disease and stroke, 807 with heart disease and diabetes, 188 with stroke and diabetes, and 275 with all three CMDs). In the multi-adjusted Cox proportional hazard models, overweight and obesity were associated with increased risk of both diabetes and CVD (**Figure 7**). Compared to normal BMI, the HR (95% CI) of overweight/obesity was 1.52 (1.45−1.58) for any CMD and 1.93 (1.76−2.13) for cardiometabolic multimorbidity.

High BMI and CMDs in CMD-discordant twin pairs. In the stratified Cox hazard model, overweight/obesity was still associated with a higher risk of CMDs among 729 CMD-discordant twin pairs (1.37 [1.18−1.61]), which was similar to the effect observed among the total population. The HRs (95% CIs) of developing CMDs were 1.47 (1.22−1.78) and 1.15 (0.87−1.54) for dizygotic and monozygotic twin pairs, separately. There was no statistically significant difference of the HRs between the dizygotic and monozygotic twin pairs (P = 0.12).

BMI categories	No. of subjects	Cases Person-years	HR (95% CI)
Cardiometabolic diseases			
Underweight	1954	436/23642	0.92 (0.81-1.04)
Normal BMI	18473	4642/228304	Reference
Overweight/obesity	16195	6124/186868	1.52 (1.45-1.58)
Overweight	13484	4841/157786	1.40 (1.33-1.46)
Obesity	2711	1283/29082	2.15 (2.01-2.30)
Cardiometabolic multimorbidity			
Underweight	1597	79/20946	0.87 (0.64-1.17)
Normal BMI	14779	948/200438	Reference
Overweight/obesity	11630	1559/154766	1.93 (1.76-2.13)
Overweight	9840	1197/131823	1.69 (1.52-1.87)
Obesity	1790	362/22943	3.28 (2.85-3.76)
Type 2 diabetes			
Underweight	1954	30/25330	0.43 (0.27-0.63)
Normal BMI	18473	693/249279	Reference
Overweight/obesity	16195	2162/210529	3.59 (3.28-3.94)
Overweight	13484	1482/177680	2.77 (2.51-3.05)
Obesity	2711	680/32849	6.99 (6.23-7.83)
Cardiovascular disease			
Underweight	1954	418/23737	1.00 (0.88-1.12)
Normal BMI	18473	4275/230448	Reference
Overweight/obesity	16195	4894/195167	1.21 (1.16-1.27)
Overweight	13484	4005/163208	1.18 (1.12-1.24)
Obesity	2711	889/31959	1.38 (1.27-1.49)

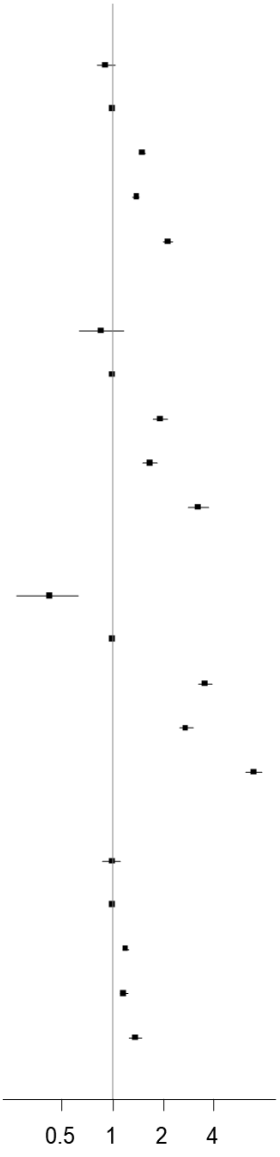

Figure 7. Associations between body mass index (BMI) and cardiometabolic diseases (CMDs).

Adjusted for age, sex, education, marital status, smoking status, alcohol consumption, physical activity, and hypertension. Cardiometabolic multimorbidity was defined as the presence of at least two CMDs.

4.2.3 Association between patterns of BMI change and CMDs

Among 20,606 participants with self-reported BMI both at baseline and 25 to 35 years before baseline, 6,388 (31.0%) developed a CMD. The presence of overweight/obesity regardless of whether it was in earlier or later life, was associated with increased risk of CMDs (**Table 4**). The risk of CMDs was higher for subjects with high BMI in both their earlier and later life than those with high BMI only in earlier or later life.

Table 4. Associations between long-term body mass index (BMI) change and cardiometabolic diseases (CMDs).

BMI in earlier and later life	No. of Subject	Cases/Person-years	HR (95% CI)[a]	HR (95% CI)[b]
Underweight-underweight	847	151/10,812	0.78 (0.66−0.92)	0.80 (0.66−0.96)
Underweight-normal	3,948	600/51,662	0.80 (0.73−0.88)	0.85 (0.76−0.94)
Normal-normal	6,305	1,971/75,460	Reference	Reference
Normal-underweight	288	119/2,899	1.22 (1.01−1.46)	1.10 (0.81−1.46)
Overweight/obesity in earlier or/and later life	9,218	3,547/105,657	1.42 (1.34−1.50)	1.42 (1.33−1.51)
Only in earlier life	339	172/3110	1.20 (1.02−1.39)	1.28 (1.02−1.59)
Only in later life	6,811	2,227/81,528	1.34 (1.26−1.43)	1.33 (1.24−1.43)
Both in earlier and later life	2,068	1,148/21,019	1.65 (1.53−1.78)	1.69 (1.55−1.85)

This table is produced from Guo et al. Clinical Nutrition 2021 (145).
HR, hazard ratio; CI, confidence interval.
[a] Adjusted for age and sex.
[b] Additionally adjusted for education, marital status, smoking status, alcohol consumption, physical activity, and hypertension.

4.2.4 Joint effect of healthy lifestyle and high BMI on CMDs

Compared to participants with normal BMI and a favorable lifestyle, those with overweight/obesity and an unfavorable lifestyle had a higher CMD risk (2.20 [2.03−2.38]), followed by those with overweight/obesity but a favorable lifestyle (1.51 [1.44−1.58]) and those with normal BMI but an unfavorable lifestyle (1.41 [1.28−1.56]) (**Figure 8**). Among participants with overweight/obesity, a favorable lifestyle was associated with a lower CMD risk than an unfavorable lifestyle (0.68 [0.64−0.74]). The additive interaction between lifestyle and BMI was statistically significant (RERI 0.28, 95% CI 0.07−0.49).

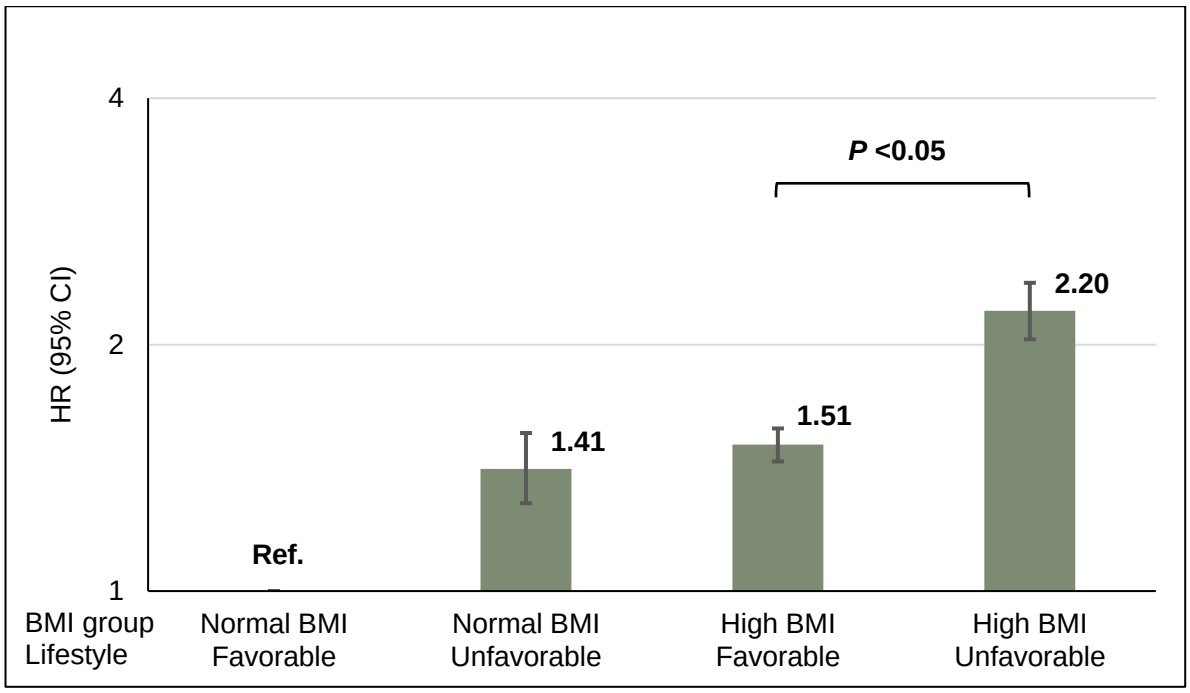

Figure 8. The joint effect of lifestyle and body mass index (BMI) on the risk of cardiometabolic diseases (CMDs).

HR, hazard ratio; CI, confidence interval. Normal BMI was defined as BMI 20—<25 kg/m^2 and high BMI was defined as BMI ≥25 kg/m^2. Favorable lifestyle was defined as any two or three of the following: not smoking, no or mild alcohol consumption, and regular physical activity. Adjusted for age, sex, education, marital status, and hypertension.

4.3 Late-life weight change and dementia (Study III)

4.3.1 Population characteristics

Of the 1,673 participants without dementia from SNAC-K, the mean age at baseline was 69.4 (SD = 8.7) years, and 1,029 (61.5%) were female. Compared to participants without dementia during the follow-up, those with incident dementia were more likely to be older, less educated, physically inactive, have CVDs and hypertension, and be *APOE* ε4 carriers (*P* <0.05 for all). Compared to participants with stable BMI (i.e., ≤5%), those with BMI loss >10% were older, less educated, physically inactive, and had a higher prevalence of hypertension, CVDs, and depression, while those with BMI gain >10% were younger (*P* <0.05 for all).

4.3.2 Association between BMI change and dementia

Over the follow-up (median 5.78 years, interquartile range: 5.39 to 5.94 years), 102 dementia cases occurred. **Figure 9** shows a U-shaped association between BMI change and dementia. Compared to participants with a stable BMI, the HR of dementia increased significantly with

a large loss or gain in BMI (2.93 [1.72−4.91] and 2.61 [1.09−5.54], respectively). Moreover, there were U-shaped associations between BMI and dementia subtypes, including Alzheimer's disease dementia and vascular dementia.

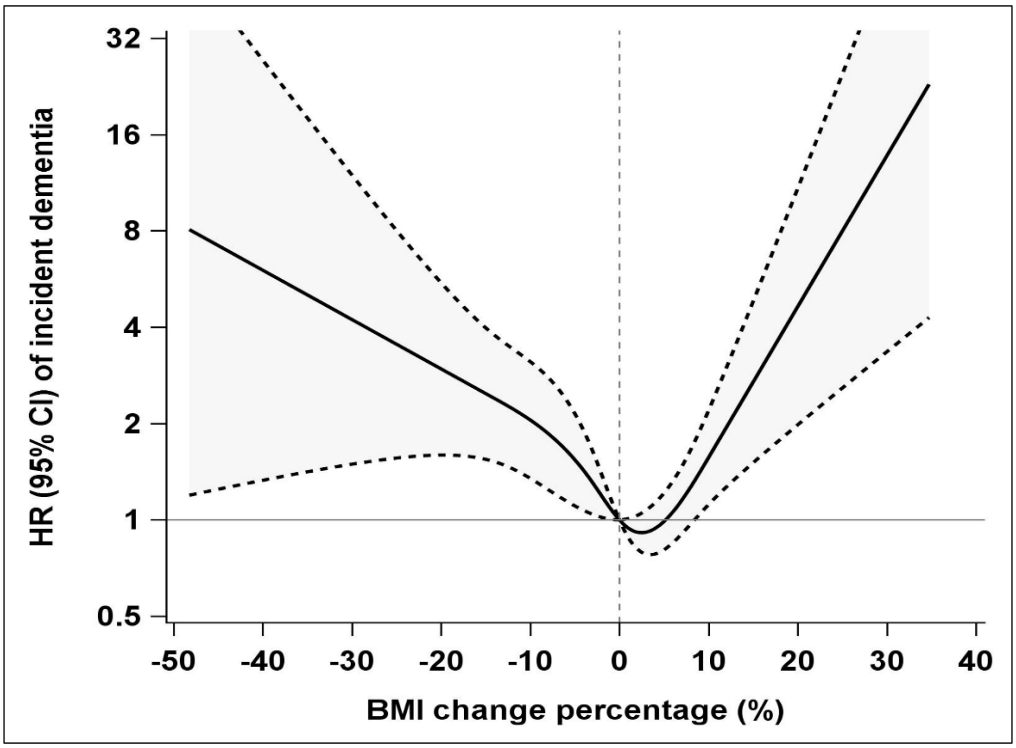

Figure 9. Associations between body mass index (BMI) change over 6 years and the risk of incident dementia.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using multivariable Cox regression models with restricted cubic splines. Risk estimates were adjusted for baseline age, sex, education, smoking status, alcohol consumption, physical activity, medical history of cardiovascular diseases, hypertension, diabetes, depression, and *APOE* ε4 carrier status. *P* value for overall association and *P* value for non-linear association were both <0.05. This figure is produced from Guo et al. J Gerontol A Biol Sci Med Sci 2022 (146).

4.3.3 Joint effect of *APOE* genotype and BMI change on dementia

Compared to *APOE* ε4 non-carriers with stable BMI, the risk of dementia was higher among *APOE* ε4 carriers with >10% BMI loss or gain (HR = 6.66 [95% CI 2.83−14.4] and 9.93 [95% CI 3.49−24.6], respectively) (**Figure 10**). Moreover, *APOE* ε4 carriers had a higher risk of dementia compared to non-carriers (6.81 [1.52−47.4]) among those with >10% BMI gain. Among those with BMI loss >10%, *APOE* ε4 carriers had an increased risk of dementia compared to non-carriers (1.93 [0.79−4.41], *P* = 0.13), albeit the difference was not statistically significant.

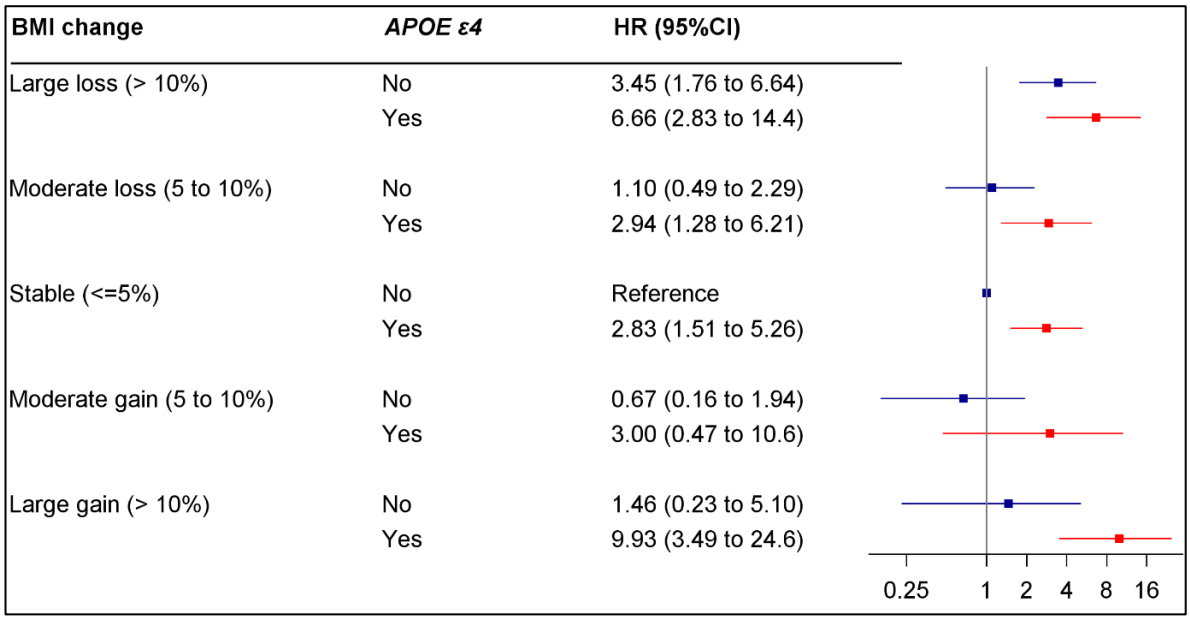

Figure 10. Joint effect of *APOE* ε4 carrier status and BMI change on incident dementia.

BMI, body mass index; APOE, apolipoprotein; HR, hazard ratio; CI, confidence interval. Adjusted for age, sex, education, smoking status, alcohol consumption, physical activity, medical history of cardiovascular diseases, hypertension, diabetes, and depression. This figure is produced from Guo et al. J Gerontol A Biol Sci Med Sci 2022 (146).

4.4 BMI and overall survival, chronic disease-free survival (Study IV)

4.4.1 Population characteristics

Among 11,597 participants aged 60-79 years free from chronic diseases (including diabetes, CVD, and cancer) at baseline, the mean age was 67.5 (SD: 5.4) years, and 6,279 (54.1%) were female. Compared to participants with normal weight, those with overweight or obesity were younger, less educated, less engaged in regular physical activity, and had a higher prevalence of hypertension and dyslipidemia (P <0.01 for all).

4.4.2 Late-life BMI and survival

Over up to 18 years of follow-up, 8,772 (75.6%) participants developed incident chronic diseases or died. Specifically, 7,913 participants developed chronic diseases and 4,050 died. Compared to normal BMI, overweight and obesity were associated with an increased risk of a composite endpoint defined as incident chronic diseases or death (HR = 1.18 [95% CI 1.12, 1.24] for overweight and 1.42 [1.30, 1.55] for obesity). Participants with high BMI had a similar overall survival at age 60 years compared to those with normal BMI, whereas those with underweight had 2.9 (95% CI 1.4, 4.4) fewer years of overall survival; the mean estimated overall survival at age 60 years was 24.2 (23.4, 25.0) years for normal weight, 24.7 (23.9, 25.4) years for overweight, and 23.1 (22.1, 24.1) years for obesity. Compared with normal BMI, the loss of chronic disease-free years was 1.1 (0.3, 2.0) years for overweight

and 2.6 (1.6, 3.5) years for obesity (**Figure 11**). In sex-specific analyses, participants with high BMI had similar overall survival as those with normal BMI. Still, they had significantly shorter chronic disease-free survival (except for males with overweight).

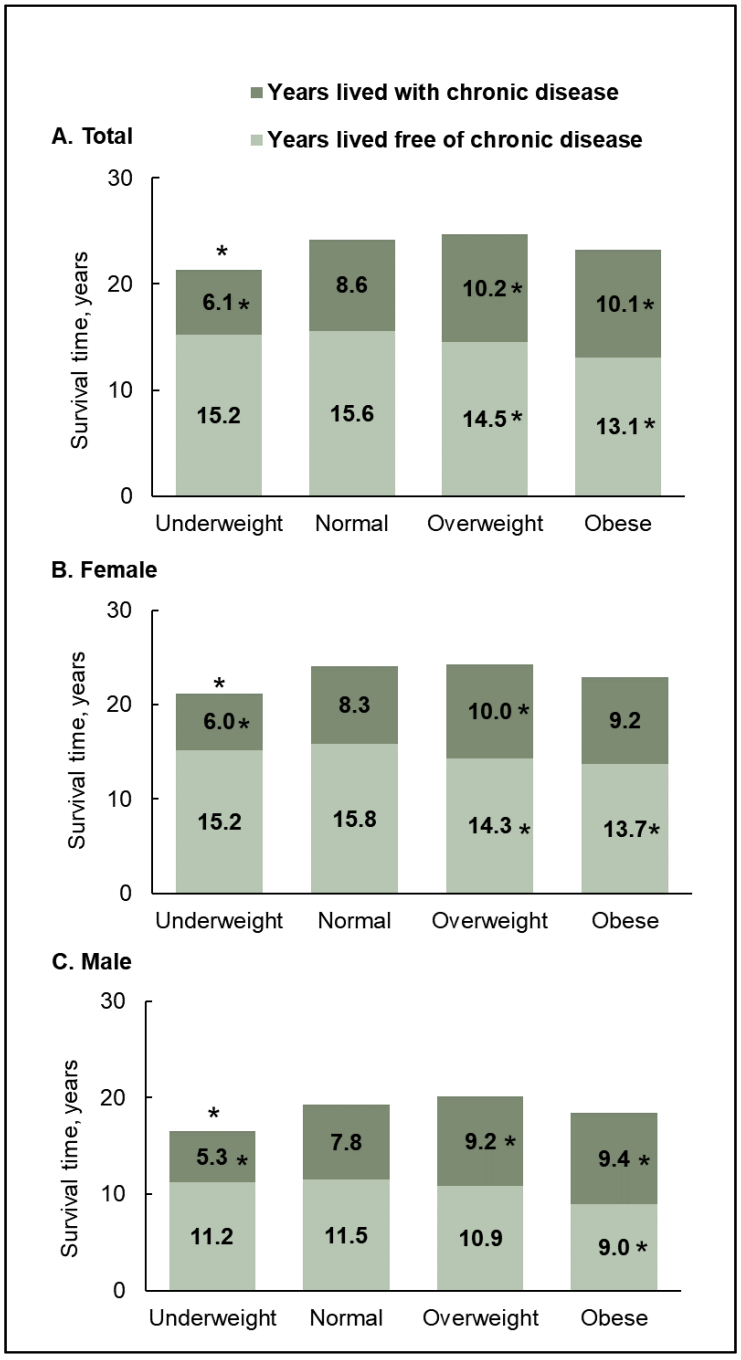

Figure 11. Years lived with and without chronic disease at age 60 years across BMI categories**.**

BMI, body mass index. Total population (panel A), female (panel B), and male (panel C). Adjusted for age, sex, education, marital status, smoking status, alcohol consumption, physical activity, hypertension, and dyslipidemia. * Compared to the normal weight, the difference of overall survival (i.e., on the top of the bar), years lived with or without chronic diseases (i.e., cardiovascular diseases, diabetes, and cancer) were significantly different among corresponding BMI groups (P <0.001).

4.4.3 Mid-to-late life BMI and survival

Compared to participants with a stable normal BMI across mid- and late life, disease-free survival among participants with consistent overweight/obesity or only midlife overweight/obesity was shortened by 2.2 (1.0, 3.4) and 2.6 (0.7, 4.4) years, respectively (**Figure 12**). Although participants with only late-life overweight/obesity had similar overall and disease-free survival as those with a stable normal BMI, they experienced 1.7 (0.1, 3.2) more years lived with chronic diseases.

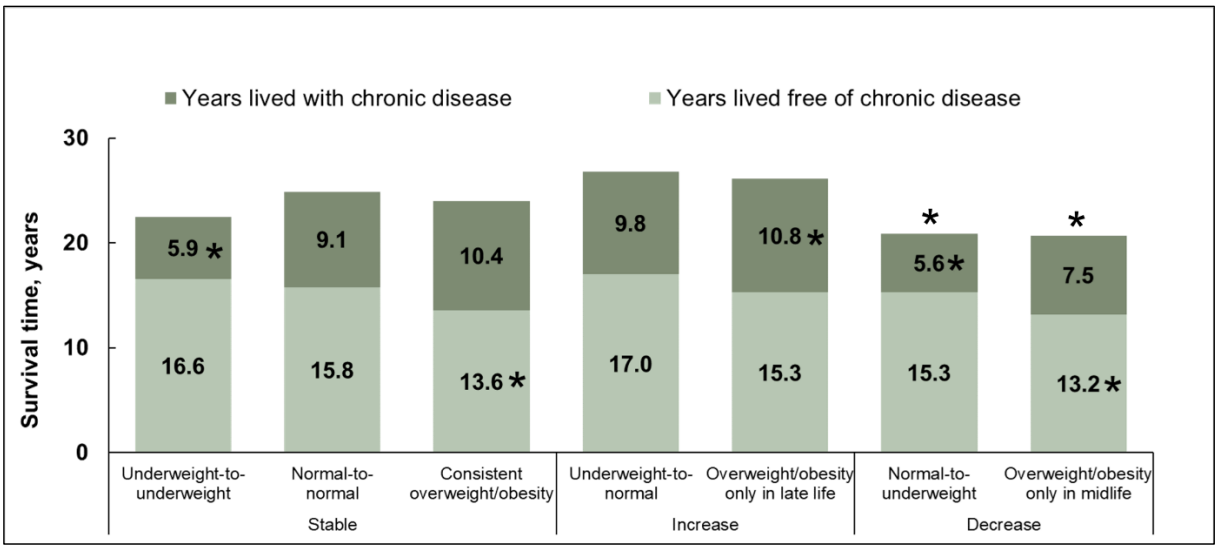

Figure 12. Overall survival, years lived with and without chronic disease at age 60 years across BMI change categories.

Adjusted for age, sex, education, marital status, smoking status, alcohol consumption, physical activity, hypertension, and dyslipidemia. * Compared to the stable normal group, the difference of overall survival (i.e., * on the top of the bar), years lived with or without chronic diseases (i.e., cardiovascular diseases, diabetes, and cancer) were significantly different among corresponding BMI change groups (*P* <0.001).

5 DISCUSSION

BMI, together with CC and MAC, declines over time in older adults. High BMI in mid or late life is associated with an increased risk of CMDs. Both large BMI loss and large BMI gain are related to an increased risk of dementia. Moreover, mid or late-life high BMI may shorten chronic disease-free survival. Together, these findings suggest that mid and late-life high BMI and substantial BMI changes can predict adverse health outcomes in old age.

5.1 Interpretation of the main findings

5.1.1 BMI, CC, and MAC trajectories

Previous cross-sectional (29,147,148) and longitudinal studies (17,23) have described BMI trajectories across the lifespan from early to late life. BMI has been reported to increase until 60 to 70 years of age, then reach a plateau and, finally, slightly decline after 80 years of age. Consistent with previous findings, in *Study I*, BMI remained stable or declined slightly over the 15-year follow-up in younger-old participants (60 to 72 years), whereas there was a steeper BMI decline in older-old participants (≥78 years). BMI consists of not only fat mass but also muscle mass; this is a crucial point to consider when interpreting changes in BMI. Findings from the literature about fat and muscle mass changes in aging suggest that the two may follow different patterns. Fat mass tends to increase and peak between 70 and 80 years, whereas muscle mass decreases after the age of 50 years (148–150). Therefore, it is plausible that the decline in BMI observed in *Study I* among the SNAC-K's older adults might be driven by excessive muscle mass loss. At the same time, we acknowledge that BMI might lack sensitivity in detecting slight muscle mass loss, especially in earlier late life (<80 years), and in this period the increase in fat mass may mask the decrease in muscle mass. In *Study I*, we observed that the decline in CC and MAC, two anthropometric measures suggested as proxies of muscle mass (35,151,152), began earlier and was steeper than the decline of BMI. However, the magnitudes of declines in BMI, CC, and MAC were similar in very old adults (e.g., >80 years). This result can be explained by the fact that fat mass is stable or only slightly increases among very old adults and may be less likely to mask the loss of muscle mass (149).

Progressive muscle mass loss in late life, also known as sarcopenia together with low muscle strength and poor physical performance, has been associated with an increased risk of adverse health consequences (e.g., disability and mortality) (25,26,153,154). Our findings highlight the utility of BMI, CC, and MAC as easily measured anthropometrics for monitoring and detecting accelerated muscle loss in older adults. Moreover, BMI loss in older adults may be driven by muscle mass loss rather than fat mass loss, which can help to explain the seemingly paradoxical associations between overweight and positive health outcomes, when overweight/obesity are defined in terms of BMI. As the reference, the normal BMI group might include those who begin with overweight and experience muscle loss, which can attenuate or even distort the impact of high BMI on health.

5.1.2 BMI and CMDs

The associations between overweight/obesity and CVDs or diabetes are well-established (52,55,155,156). In line with previous literature (52,55,156–158), *Study II* showed that both mid- and late-life overweight/obesity were associated with an increased risk of individual CMDs. Existing evidence has also shown that genetic and early-life environmental factors (e.g., malnutrition during fetal development and socioeconomic status during childhood) may play a role in the development of both obesity and CMDs in later life (61,159–161). Taking advantage of the co-twin study design, our findings showed that the BMI-CMD associations still existed after controlling for shared familial factors. The results suggested that high BMI could serve as a CMD risk predictor for CMDs even among individual with the same genetic background and early-life environment.

Moreover, existing evidence has shown that cardiometabolic multimorbidity (i.e., having ≥2 CMDs) is related to a higher risk of adverse health consequences, such as dementia and mortality, compared to having a single CMD (48,49). The increased prevalence of cardiometabolic multimorbidity has been a growing public health problem with the aging population. In a pooled analysis of 16 cohorts from the United States and Europe, the risk of cardiometabolic multimorbidity among adults with overweight or obesity was more than 2-times higher than those with normal BMI (56). Similarly, in *Study II*, participants with high BMI had almost 2-times higher risk of cardiometabolic multimorbidity than those with normal BMI. In summary, our findings highlighted that high BMI might represent a risk factor not only for individual CMDs such as diabetes or heart diseases, but especially for their comorbid forms—likely reflecting the severity of the person's cardiometabolic health. Moreover, individuals with overweight/obesity and a single CMD may benefit from the effective prevention of and active screening of comorbidity to reduce further severe consequences like dementia and premature death.

5.1.3 BMI and chronic disease-free survival

A large body of evidence, as well as our *Study II*, has pointed to high late-life BMI as a risk factor for major chronic diseases, including diabetes, CVDs, and cancer (55,124,162,163). Although these chronic diseases are the most common causes of reduced lifespan (164), the extent to which late-life BMI is related to mortality is still debated (14). Previous studies have described a J-shaped association between BMI and mortality in the general older population, and the nadir of mortality was observed to be in the normal BMI range (around 24 kg/m^2) (10) or in the overweight range (9,165). Moreover, among individuals diagnosed with chronic diseases, overweight and obesity have been related to more favorable clinical prognoses than normal BMI—a phenomenon referred to as the "obesity paradox" (118–121). One likely explanation for the "obesity paradox" is that normal BMI—the reference group when calculating the relative risk—is a heterogeneous health entity. In addition to people with a healthy weight, the normal BMI group may also include those who formerly had overweight/obesity but transitioned to a normal BMI because of adverse health conditions or near death (23,166). Our *Study I* also indicated that vascular disorders and diabetes were associated with accelerated weight loss. Therefore, unintentional weight loss may attenuate or

even distort the BMI-mortality association. A study design accounting for the influence of overweight and obesity on the progression from a healthy state to the development of chronic diseases and ultimately death may help address the challenge of managing weight to extend life expectancy and, more importantly, to promote disease-free survival. Several studies have attempted this, using various definitions for disease-free survival. Some of them considered only one type of disease, such as survival free from diabetes (124) or CVD (54,123,127,167–169). Others focused on a wide range of non-communicable diseases (e.g., two or more of the following: diabetes, CVD, cancer, asthma, or chronic obstructive pulmonary disease) (125,126,128,170,171). Most studies consistently showed a disadvantage of obesity on disease-free survival (54,124,127,128). However, studies investigating the association between overweight and survival have been inconclusive. Taking CVD-free survival as an example, compared to normal BMI, overweight has been associated with a similar (127), longer (169), and shorter (54,128,167) CVD-free survival in various studies. In *Study IV*, we found comparable overall survival for normal BMI, overweight, and obesity. However, both overweight and obesity were associated with 1.1 and 2.6 fewer years of disease-free survival (i.e., years lived without diabetes, CVD, or cancer). Moreover, underweight (BMI <20 kg/m^2) was associated with shorter survival after chronic disease onset compared to normal BMI. A poor metabolic reserve may account for the poor chronic disease prognosis among the underweight. Our results suggest that keeping late-life weight within the normal BMI range can extend both lifespan and years lived in good health.

5.1.4 Late-life BMI change and dementia

In *Study III*, we found a U-shaped association between BMI change and dementia. Both large BMI loss and gain (change >10%) in late life were related to about two-fold higher dementia risk than stable BMI. Similarly, most previous studies on this topic have reported that compared to stable weight, weight loss in older adults is associated with an increased risk of dementia (89–91,93,94,96–98,172); however, one study found a non-significant association between weight loss and dementia (92). The evidence on the relationship between weight gain and dementia is mixed. Although some studies observed that weight gain in old age was associated with a lower risk of dementia or showed non-significant impacts on dementia (89,90,95–98), others have pointed to a higher dementia risk with weight gain (92–94). These discrepancies could be due to methodological issues. The small sample size for the group of participants with large weight gain may limit the power to detect statistically significant associations (173). Also, large but not moderate weight gain may be associated with a higher risk of dementia, as was the case in our study and a previous study (94), the lack of finer categories of weight gain may also account for the non-significant results (90,96,98).

The mechanisms underlying the links between large weight change and dementia remain unclear. Given that the neuropathological changes underlying dementia begin 10−20 years prior to the clinical diagnosis (174,175), weight loss might not be a cause but rather a consequence of underlying dementia. Impaired olfactory function and reduced appetite concomitant with neurodegenerative processes may limit energy intake and account for

accelerated weight loss (176). Another explanation is that weight loss in older adults may reflect an excessive loss of muscle mass, which can impair brain and cognitive health via muscle-brain cross-talk (177) and via their common biochemical mechanisms, involving oxidative stress, inflammation, and hormonal dysregulation (178,179). On the other hand, weight gain in late life generally reflects increased fat mass. In this case, excessive fat mass may impair cognitive health and increase the risk of dementia throughout the biological pathways linked to insulin resistance, atherosclerosis, and increased inflammation (180,181). Moreover, large BMI loss and gain could both be early signs of deteriorating global cognitive function before dementia, as indicated in our study (*Study III*, Supplementary Table 9). Although the observational study design prevented us from making any causal interpretation of the association between excessive weight change and dementia, the findings suggest that monitoring weight change regularly in old age could be considered as part of routine health practice for identifying populations at a high risk of dementia.

5.1.5 BMI change and CMDs, chronic disease-free survival

There is great interest in understanding the role of weight change over the life course in predicting adverse health outcomes. In *Study II*, we found that participants who transitioned from normal to high BMI had a higher CMD risk than those who had a consistent normal BMI, but a lower CMD risk than those who had a consistently high BMI. These findings are consistent with previous literature showing that weight gain confers CMD risk (182,183) and in line with well-demonstrated beneficial effect of weight loss for CMD (183–185). We, however, observed that adults with high BMI in their earlier life but normal BMI in later life still had a higher CMD risk than those with a consistently normal BMI, indicating that weight reduction cannot completely counteract the risk of CMDs resulting from previous overweight or obesity. Other studies have reported similar results (18,183,186), though others denoted that weight loss can reverse the adverse risk of overweight or obesity (187) and even add more benefits (e.g., the risk of diabetes, hypertension, and dyslipidemia after weight loss was lower among individuals with obesity compared to those with a stable lower BMI) (184). In our study, we could not distinguish between intentional weight loss (e.g., due to lifestyle modifications or bariatric surgery) and unintentional weight loss (e.g., due to aging, smoking, or wasting disease). Unintentional weight loss may mask the benefits of intentional weight loss for preventing CMDs (188). Alternatively, the worse cardiometabolic risk profiles (e.g., insulin resistance, carotid intima-media thickness) that arise from excess weight may persist even after weight reduction (18). In other words, there may be a residual risk of CMDs from previous overweight or obesity, even among individuals who subsequently transitioned to a normal BMI. Another consideration is that those individuals may receive less medical attention than those who currently have overweight or obesity.

Moreover, consistent overweight/obesity from earlier to later life contributed to a higher CMDs risk than the presence of overweight/obesity in only earlier or later life. This finding supports the notion that consistent overweight or obesity has adverse accumulating effects on cardiometabolic health (189–192). This result highlights the excessive CMD risk due to continuing failure to tackle high BMI and the benefits of preventing overweight and obesity during any period over the life course.

In *Study IV,* we examined mid-to-late life BMI transitions in relation to absolute survival time in terms of years lived with or without chronic diseases (i.e., diabetes, CVD, and cancer). Compared to those with a stable normal BMI, people with consistent overweight/obesity from mid-to-late life had 2.2 fewer years of chronic disease-free survival. Those who transitioned from midlife high BMI to late-life normal BMI had 4.2 years shorter overall survival, of which 2.6 years were due to loss of disease-free survival. Although an increase from normal BMI in midlife to high BMI in late life seemed to be harmless to the overall and disease-free survival, it can extend 1.7 more years of living with chronic diseases and burden the healthcare system.

Our findings emphasize the importance of lifetime prevention of high BMI to reduce the risk of chronic diseases and to extend healthy survival—the earlier the prevention of overweight and obesity, the more beneficial for health. Moreover, it is critical to consider not only an individual's current BMI but also their historical BMI over the life course as the health effects of overweight/obesity may not be felt immediately but rather manifest themselves cumulatively over time.

5.1.6 Modifiable factors decelerating BMI decline and attenuating high BMI-related risk of CMDs

Given that considerable weight loss in older adults, usually driven by muscle loss, is associated with adverse health outcomes (129,193), research is warranted to identify the modifiable lifestyle factors that support the maintenance of muscle mass in older adults or at least decelerate muscle mass loss. In *Study I,* we identified that older adults with high educational attainment and a lifestyle characterized by regular physically activity had minimal decreases in BMI, CC, and MAC, independent of the presence of diabetes and vascular disorders.

Several studies also showed that older adults with high education had slower weight loss or muscle mass loss (194,195). Physical activity in young and middle-aged adults has been recommended to prevent weight gain. In late life, however, more attention is posed to the beneficial effect of physical activity on preserving muscle mass and preventing excessive weight loss (37,38,196). In the *Study I,* we found that physical activity attenuated declines in BMI and CC, with a more pronounced impact among participants aged ≥78 years than those aged <78 years. This finding is consistent with previous results from the Cardiovascular Health Study, which showed that the difference in weight loss between physically active and inactive participants was more evident among those ≥81 years than those aged 65–80 years (38). However, in a previous study considering multiple factors (e.g., education, genetic risk score, midlife lifestyle factors, and chronic diseases), there was no significant association between physical activity and late-life BMI change (23). Physical activity's impact on body compositions is rather short-term and may not hold if the individual changes her/his activity level; the aforementioned study explored late-life BMI change in relation to midlife rather than late-life physical activity, which may explain the non-significant results (23). Previous studies in both humans and animals have proposed mechanisms supporting the benefits of physical activity for slowing age-related muscle mass loss via activating anabolic signaling in relation to protein synthesis (e.g., insulin-like growth factor-1) and exerting anti-oxidative

stress and anti-inflammation effects to suppress molecules associated with protein degradation (197).

In *Study II*, a favorable lifestyle was associated with an over 30% reduced risk of CMDs among participants with high BMI. This is supported by previous findings that non-smoking (76), moderate alcohol consumption (78,198), and being physically active (73,199) can attenuate CMD risks. Because the SALT study did not collect weight change information after baseline, we could not explore whether reduced CMD risk among participants with favorable lifestyles were mediated by weight loss. However, several possible biological mechanisms related to healthy lifestyles, including reduced oxidative stress, inflammation, insulin resistance, and hyperglycemia, may represent an additional bonus of a healthy lifestyle for health, regardless of weight change (200,201).

5.2 Methodological considerations

This thesis included four epidemiological studies. Like every epidemiological study, systematic error (selection bias, information bias, and confounding bias) and random error may arise, and they have consequences in terms of validity and precision. Possible sources of errors and their potential influence on the findings are discussed below.

Selection bias

Selection bias is generally introduced by non-randomly selecting the sample from the target population, leading to a non-representative sample of the target population. Therefore, the observed associations between the exposure and outcome of interest may vary between the study sample and the target population. In this thesis, we cannot rule out a biased selection of the study sample, though the response rates were relatively high (above 70%) both in SNAC-K and SALT. Individuals who agreed to participate in the SNAC-K and SALT studies may be more likely to be healthier than those who are theoretically eligible but refuse to participate; this is a common phenomenon in population-based studies, known as the *healthy volunteer effect* (202). A previous study has shown that individuals who refused to participate in the SNAC-K baseline examination had a shorter time to death than those who agreed to participate (203). In this sense, the healthy volunteer effect may lead to an underestimation of the observed associations.

Another source of selection bias can arise from missing data problems. The underlying reasons for missing data can vary, and so can their influence on the validity of results. Suppose that missing data are missing completely at random or missing at random. In that case, those with complete data information can be considered a random sample of the target population without or with conditioning on other known variables. In SNAC-K and SALT, there were participants with missing data for some variables at baseline (e.g., missing information about education, marital status, or lifestyle factors), which were generally missing at random. This type of missing data is relatively benign and may not bias the estimates of the associations. In all four studies, in addition to conducting analyses among participants with complete data, we further performed sensitivity analyses after imputing the missing data. Results did not change substantially.

For data that are missing not at random, participants with missing data may differ in important ways compared to those with complete data. This can complicate the analyses. For example, in *Study I*, we examined the trajectories of three anthropometric measures and included participants with baseline measurements of BMI, CC, and MAC, as well as at least one repeated measurement over follow-up. Of 716 participants without repeated measurements, 329 (46%) were due to drop-out before the first follow-up examination. Participants who dropped out were more likely to be older, less educated, less physically active, and had vascular disorders and diabetes at baseline compared to those who remained in the study. Suppose that these participants who dropped out were also more likely to experience accelerated declines in BMI, CC, and MAC. This selection process would influence not only these trajectories of the anthropometric measures but also distributions of determinants possibly predicting these trajectories. Both of which would result in underestimations of the observed associations.

Drop-out can also influence the ascertainment of dementia in *Study III* because diagnoses of dementia were mainly dependent on the follow-up assessment. The drop-out rate over the 12-year follow-up in SNAC-K is around 21% (719/3363), which is relatively low. If participants dropped out due to impaired cognitive function, those who remained in the risk set during the follow-up are more likely to be those with better cognitive function and low risk of dementia. However, we compared the MMSE between those who participated and those who dropped out, and the difference was negligible (28.2 vs. 28.0, different = 0.24, *P* = 0.96). Therefore, the loss of follow-up may not largely bias the results of *Study III*. For *Studies II and IV* using data from SALT, the impact of drop-out is of less concern because outcomes in SALT were obtained from health registers.

Confounding bias

Confounding is a confusion of effects and a fundamental problem of causal inference in observational studies. Generally, a factor can be considered a confounder if it is the common cause of exposure and outcomes based on causal diagrams (Directed Acyclic Graphs). The true impact of exposure on outcomes can be overestimated, underestimated, or even reversed. In all four studies, a wide range of potential confounders have been considered. In addition, in *Study II*, which used a twin study design, analyses conducted among co-twin pairs can further address the confounding effect of shared familial factors, which are generally unavailable in epidemiological studies. However, the possibility of unmeasured confounding due to unavailable or unknown factors still exists and cannot be ruled out.

To understand the impact of unmeasured/unknown confounder on our results, we calculated the E-values in *Study II, III, and IV*. Briefly, the E-value provides information on the minimum strength of the associations (on the risk ratio scale) that the unmeasured confounder would need to have with both the exposure and the outcome in order to explain away the observed exposure-outcome association (204). Therefore, the higher the E-values, the lower the probability that unmeasured confounders would explain away the observed associations. In *Study II,* the E-value is 2.01 (95% CI 1.90−2.09). This indicates that to fully explain away the observed associations between overweight/obesity and any of CMDs, a set of unmeasured confounders would have to be associated with a 2-fold increase in the risk of any CMDs and must be 2-times more prevalent in people with overweight/obesity than normal BMI after adjusting all measured covariates. Taking the dietary patterns as an example of the

unmeasured confounder, the risk ratio of the associations between unhealthy dietary pattern and overweight/obesity (OR=1.65; 95% CI: 1.45−1.87 from a review paper) (205), and between dietary and cardiometabolic diseases were below 2 (206,207). Therefore, accounting for the confounding effect of dietary patterns is less likely to explain away the observed associations in our study. Moreover, considering that favorable lifestyles (e.g., non-smokers, physical activity, healthy diets) tend to cluster together in the same individual, the confounding effect of dietary patterns on the BMI-CMDs associations could be partly controlled for by adjusting for other lifestyle factors. In *Study III & IV*, the E-values for the effect estimates (i.e., the association between BMI change and dementia, and between late-life BMI and chronic diseases or death) were relatively high (range from 1.50 to 5.31), indicating that unmeasured confounders were less likely to explain away these observed associations.

Information bias

Information bias, also known as misclassification, arises from inaccurately measured variables (e.g., exposure and outcome) and can occur either differentially or non-differentially. Differential misclassification means that the misclassification depends on the variables of interest, which may lead to either exaggerated or underestimated associations. Non-differential misclassification means that the misclassification does not rely on the status of the participant with respect to exposure, outcome, and other variables in the analysis, which may lead to underestimated associations.

Ascertainment of BMI. In SNAC-K, for most of the participants, BMI was calculated using weight and height measured by trained staff, except for a sub-sample population (n = 462) with only self-reported BMI. In SALT, BMI was self-reported for all participants. However, the correlation between self-reported and measured BMI was relatively high in SNAC-K (correlation coefficient = 0.95) (144) and in STR (correlation coefficient was 0.97 for height and 0.95 for weight) (208). Thus, BMI misclassification may be subtle in our study populations and unlikely to largely alter our results.

Another concern about BMI is its limits as a proxy of body fat. Commonly used BMI cut-off values to diagnose overweight and obesity have high specificity but poor sensitivity (209). That is, the normal BMI group may include both healthy normal adults and unhealthy ones with excessive fat mass, which may attenuate the impact of high BMI on outcomes in *Studies II & IV.* The bias of BMI for predicting body fat may be differential depending on variables such as age and sex (210). However, controlling those variables in the model can help deal with the differential misclassification.

Ascertainment of diseases. In SNAC-K, medical conditions (e.g., heart disease, stroke, diabetes, and dementia) were ascertained following standard procedure through multiple sources, including self-reported information, clinical examinations performed by physicians, laboratory blood sample tests, and medical records from the Swedish NPR and death register. Therefore, the misclassification of diseases, if any, is more likely non-differential, which may lead to an underestimation of the associations reported in *Studies I & III.*

In SALT, information about diseases (e.g., heart disease, stroke, diabetes, and cancer) was obtained via the linkage to the Swedish health registers. Evaluations of the Swedish inpatient register came up with high positive predictive values for most diagnoses of heart disease,

stroke, and diabetes (85-95%) (211), and high sensitivity for heart disease (80%) and stroke (90%) but not for diabetes (211,212). Although in *Study II & IV,* the outpatient and drug registers were also used to minimize the underreported cases, registers may be prone to capture severe diseases instead of asymptomatic diseases. Therefore, the results of *Study II & IV* may be more likely to reflect the association between BMI and severe diseases. Moreover, people with overweight or obesity may receive more careful monitoring and frequent health check than those with normal BMI. Thus, they may be diagnosed with dementia earlier and are less likely to have undiagnosed dementia.

Ascertainment of other variables. Lifestyle factors, including smoking status, alcohol consumption, and physical activity, were self-reported instead of objectively measured. It is possible that participants with unfavorable lifestyles were misclassified as having a favorable lifestyle. This information bias would dilute the benefits of favorable lifestyle factors for preventing the decline in BMI, CC, and MAC in *Study I*, and for preventing CMDs among individuals with overweight and obesity in *Study II*.

Generalization

The SNAC-K population in the Kungsholmen district of central Stockholm has a higher socioeconomic status, such as a high education level, than the overall Swedish population. The Swedish twin population is also different from the non-twin population concerning the intrauterine environment and specific genetic factors related to twin births. Moreover, the quality of the Swedish healthcare system is better and life expectancy in Sweden is higher than most. Therefore, findings from our studies should be generalized to other populations with caution.

Random errors

Random errors resulting from measurement errors may impact the precision of our results. Although all information in the study was collected by trained staff using structured questionnaires, participants may have a varied understanding of the questions and options, independent of the BMI level and the outcomes. The large sample size could minimize random error to some degree. Moreover, all our results include point estimates with standard deviations or 95% confidence intervals to capture the variation due to random errors.

6 CONCLUSIONS

I. Among older adults, BMI, CC, and MAC declined over time, with the latter two declining earlier and faster than BMI. Cardiometabolic disorders may accelerate these declines, whereas having a higher education level or being physically active can counteract such declines.

II. High BMI was associated with an increased risk of CMDs, which cannot be explained away by the shared genetic and early-life environmental factors related to both BMI and CMDs. The risk of CMDs was highest among adults who had overweight/obesity consistently from earlier to later life, followed by those with high BMI only in earlier or later life. A favorable lifestyle may attenuate the risk of CMDs in relation to high BMI.

III. There is a U-shaped association between BMI change and subsequent dementia in older adults. Both large loss and large gain in BMI were associated with a 3-fold higher risk of dementia. Moreover, *APOE* ε4 genotype may exacerbate the dementia risk related to large BMI change.

IV. Older adults with high BMI had shorter disease-free survival than those with normal BMI, albeit similar overall survival. From mid through late life, participants with consistent high BMI and those with high BMI only in midlife had shorter chronic disease-free survival than those who remained normal.

7 IMPLICATIONS

Obesity is still a major public health concern, contributing to the risk of a wide range of diseases as well as mortality (165). The epidemic of obesity has not been adequately controlled and the prevalence of obesity continues to rise even at an increased rate (213). Among older adults, the health effects of obesity are even more complicated. Both excessive adipose tissue and loss of muscle mass contributes to adverse health outcomes. The current confusion around the health consequences of high BMI among older adults illustrates the need for a better understanding of the health risk of lifetime high BMI and how best to use BMI for predicting health problems. This thesis provides a more comprehensive understanding of patterns of BMI trajectory among older adults. It expands previous literature by investigating the health risk of weight change and long-term BMI patterns across the life course.

In this thesis, we showed the trajectories of BMI, CC, and MAC over the same time period, with CC and MAC declining earlier and more steeply than BMI. Our findings suggest that the decline in BMI in older adults is most likely driven by muscle mass loss. Therefore, monitoring changes in CC and MAC besides BMI can help identify individuals who suffer from excessive muscle mass loss in late life and thus support early interventions to prevent or slow muscle loss related disorders (e.g., disability). Our findings also highlight that several factors related to the trajectory of these anthropometric measures, such as education, physical activity and cardiometabolic disorders. The findings provide evidence for future interventions aiming to decelerate weight or muscle mass loss and for regular screenings of muscle mass for high-risk populations (such as older adults with diabetes or vascular disorders). We further investigated the impact of late-life BMI change on dementia, finding a U-shaped relationship. This result highlights the importance of late-life BMI change as an indicator of dementia. Factors associated with weight maintenance, such as physical activity shown in *Study I*, may be beneficial in reducing dementia risk and should be evaluated and verified among older adults.

Using a twin study design, we found that high BMI is associated with an increased risk of CMDs independent of genetic background and early-life environment. Our findings indicate that there might be residual risk of previous high BMI status and excessive risk of continuing high BMI status. Those results support BMI as a modifiable factor for alleviating the risk of chronic diseases and highlight the importance of preventing high BMI over the lifespan to extend healthy survival. Our results showed that in addition to the benefits of preventing high BMI, a favorable lifestyle might also account for the reduced cardiometabolic risks even among those with high BMI.

As life expectancy extends, older adults are more likely to develop cardiometabolic multimorbidity, which accounts for higher risk of adverse health consequences than individual CMDs. Our findings underscore the need for preventing the development of cardiometabolic multimorbidity among individuals with high BMI who already have a single CMD.

Taken together, this thesis highlights that, among older adults, keeping a normal and primarily stable BMI may prevent detrimental health outcomes and extend healthy lifespan.

8 FUTURE PERSPECTIVE

There is an ongoing debate on the usefulness of BMI as an indicator of obesity in geriatric practice, partly stemming from inconsistent findings on the associations between late-life high BMI and health outcomes. As a readily obtained and widely investigated anthropometric, BMI should not be dismissed in old age. Rather, future research should clarify the contribution of BMI to various age-related health outcomes, rethinking BMI as not a stable measure but rather a dynamic one over the life course.

The medical content underlying BMI in old age is complex. Fat distribution, muscle mass, and metabolic health status have been linked with different health risks (e.g., CVD and mortality) even among older adults with normal BMI (214,215). There is a need for more research to understand whether and to what extent these dimensions can improve the risk stratification of BMI, both in the general older population and among those with prevalent diseases. Moreover, unintentional BMI loss, mainly driven by muscle loss, is common in late life, and future studies are warranted to elucidate the mechanisms underlying BMI or muscle mass loss and its links to poor health conditions, guiding preventive strategies. Body composition (e.g., fat and muscle mass) can now be measured directly with the development of technology (e.g., dual-energy X-ray absorptiometry). Still, most of these methods are more technically demanding, not portable, or expensive, which limits their use in health practice. More studies are needed to identify valid and simple proxies of body composition to promote their translations into routine care for monitoring and assessing risk burden.

As shown in this thesis, lifetime BMI change patterns can be important in understanding an individual's risk profile in old age. Future studies, based on longitudinal measurements over the life span, are warranted to identify the time periods in the life course in which the effects of high BMI are most detrimental and to link varied BMI trajectories with health outcomes. Future studies should also determine whether weight-loss interventions targeting the appropriate time window can maximize their benefit for reducing obesity-related conditions.

In this thesis, we noted that large weight loss and large weight gain both contribute to an increased risk of dementia. Future studies containing data on brain pathologies (e.g., Alzheimer's disease pathology) are warranted to elucidate the mechanisms underlying the associations between weight change and dementing disorders. To figure out whether the impact of weight gain on dementia is mediated by its related cardiometabolic disorders, further studies with a sufficient follow-up, covering the process from weight gain to its related cardiometabolic conditions and to dementia, are needed.

This thesis also shows that high BMI is associated with CMDs and reduced disease-free survival in older adults. Previous studies have shown the health benefits of intentional weight loss via improving the dietary behaviors (e.g., nutritional patterns, caloric restriction, and time-restricted eating) and physical activity (e.g., resistance training and aerobic exercise) (216,217). However, there is limited evidence on the benefits of weight reduction among older-old individuals (>80 years), those suffering from multimorbidity, or those with limited physical function. The degree of weight loss that would be clinically meaningful among these populations has not been elucidated. Weight loss usually comes at the expense of muscle and bone mass loss in old age, which might counteract the benefits of weight loss in old age. Further research is required to identify more effective strategies to prevent weight gain and obesity-related health problems among older adults and to minimize their relevant harms.

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11 APPENDICES

11.1 Summary of studies on the trajectories of anthropometrics and body compositions.

Reference	Study population	Measurement	Study design	Results
Kyle UG et al. 2001 (147),Switzerland	2735 healthy white men and 2490 healthy white women, aged 15 to 98	Fat mass and fat free mass from BIA, BMI, weight	Cross-sectional study	BMI and weight increased from age 15-24 to 65-74 y and decreased after that in women and men; Fat-free mass peaked at age 35-44 y in men and at age 45-54 y in women and then decreased; Fat mass peaked at age 65-74 y both in men and women and then decreased.
Dziura J et al. 2004 (37), US	2300 people aged ≥65 from the Yale Health and Aging study	Weight self-reported annually	Longitudinal study with 8-year follow-up	Weight declines over time
Kyle, UG et al. 2006 (218), Switzerland	131 healthy adults aged >45 years	Weight, fat-free mass and body fat from BIA measured at least twice at an interval of 7 to 9 years	Longitudinal study with 8-year follow-up	In men, body fat increased 1.2 ± 2.9 kg; In women, fat-free mass decreased 0.7 ± 1.4 kg and body fat increased 1.8 ± 3.0 kg.
Raguso, CA et al. 2006 (219), Switzerland	74 men and 66 women aged ≥65	Weight, BMI, fat mass, FFST, and ASMM measured by DXA	Longitudinal study with 3 years follow-up	Differences in measures over 3 years: Weight: 0.6 ± 1.9 kg, p = 0.11; BMI: 0.4 ± 1.0 kg/m2, p <0.01; Fat mass: 0.6 ± 2.2 kg, p <0.01; FFST: -0.3 ± 1.4 kg, p =0.01; ASMM: -0.2 ± 0.9 kg, p<0.01;
Coin A et al. 2008 (148), Italy	1866 healthy Italian adults aged 20 to 80	BMI, FFMI, FMI measured by DXA	Cross-sectional study	BMI (kg/m^2) peaked at age 60-70 years and then slightly declined at age 70-80 years; FFMI (kg/m^2) peaked at age 50-69 years and then decreased; FMI (kg/m^2) peaked at age 60-69 years and kept stable at age 70-80 years

Reference	Study population	Measurement	Study design	Results
Borrud LG et al. 2010 (149), US	22,010 individuals aged ≥8 years from NHANES 1999-2004	Fat mass and fat free mass measured by DXA	Cross-sectional study	Fat mass peaked at age 60-79 then kept stable or slightly declined; Fat-free mass peaked at age 40–59 years and then declined.
Stephen WC et al. 2010 (38), US	4512 community-dwelling older (≥65 years) men and women from the Cardiovascular Health Study	Weight measured annually	Longitudinal study with 8 years follow-up	Body weight declined in a curvilinear manner over the 8 years;
Meeuwsen S et al. 2010 (220), UK	23,627 adults aged 18 to 99	BMI, fat mass and fat-free mass measured by BIA	Cross-sectional study	BMI progressively increased with age in women (from age 18 years to 70+ years) and plateaued between 40 and 70 years in men; Fat mass increased with age in women and men from age 18 years to 70+ years; Fat-free mass declined from age 40 until 60 years and then levelled off in women; fat-free mass plateaued around age 50 years and then declined after that.
Jackson AS et al. 2012 (17), US	7265 healthy men aged 20 to 96	Fat mass and fat-free mass measured by hydrostatic weighing or skinfold thickness, weight, BMI	Longitudinal study	Weight increased with aging and levelled off at age 69 years; Fat mass increased with aging, levelled off and then decreased around 80 years; Fat-free mass increased up to 50 years and then decreased; BMI increased with aging and then levelled off and then decreased around 80 years.
Gába A et al. 2014 (29), Czech	1970 healthy women aged 18-89 years	BIA measured fat mass, fat free mass, weight, BMI	Cross-sectional study	Fat-free mass peaked among women aged 40-49 years then decreased; Fat mass increased with aging; weight increased until 40-49 years, then levelled off and slightly decline after 70 years; BMI increased until 50-59 years, then slightly increase.

Reference	Study population	Measurement	Study design	Results
Dahl AK et al. 2014 (23), Sweden	6130 participants from TwinGene and 536 from SATSA	BMI, up to seven assessments for the TwinGene and up to 12 assessments for the SATSA	Longitudinal study, up to 65 years follow-up	BMI increased from the age of 25 to 65 years, and then leveled out and started to decline after the age of 80 years.
Rathnayake N et al. 2022 (150), Sri Lanka	784 healthy women aged 20–80 years from the Southern province, Sri Lanka	Fat mass and fat-free mass measured by DXA	Cross-sectional study	Fat mass increase with aging before 50 years and then levelled off or increased not significantly after (last age group ≥60 years); Fat free mass increased with aging until 50 years and the decrease after 50 years.

BIA, bioimpedance analysis; FFST, fat-free soft tissue; ASMM, appendicular skeletal muscle mass; DXA, dual-energy X-ray absorptiometry; FFMI, fat-free mass index; FMI, fat mass index; SATSA, the Swedish Adoption/Twin Study of Aging.

11.2 Summary of studies on the associations between overweight/obesity and cardiometabolic multimorbidity.

Reference	Study population	Exposure [a]	Follow-up	Covariates	Cardiometabolic multimorbidity	Results
Singh-Manoux A et al. 2018 (55), UK	8,270 adults aged 50	Measured weight and height	Mean follow-up of 23.7 years	Age, sex, ethnicity, marital status, birth cohort	Clinical examination and medical record	≥25 vs. <25 kg/m^2: HR (95% CI) = 1.79 (1.50, 2.14)
Kivimäki M et al. 2017 (56), USA and Europe	120,813 adults (mean age 51·4 years)	Measured or self-reported weight and height	Mean follow-up of 10.7 years	Age, sex, ethnic origin, physical activity, smoking status, alcohol consumption	Clinical examination and medical record	35-50 years Underweight (<20): OR (95% CI) = 0.8 (0.2, 2.5) Healthy (20·0–24·9): Ref. Overweight (25·0–29·9): 2.8 (1.9, 4.2) Class I obesity (30·0–34·9): 6.5 (4.1, 10.3) Class II-III obesity (≥35·0): 17.2 (10.2, 29.0) ≥ 50 years Underweight: 0.6 (0.4, 1.0) Healthy: Ref. Overweight: 1.9 (1.6, 2.1) Class I obesity: 3.8 (3.2, 4.5) Class II-III obesity: 10.2 (8.1, 12.8)
Xu X et al. 2018 (57), Australia	13,714 women aged 45–50	Self-reported weight and height	Over 20 years	Age, time period, country of birth, marital status, socioeconomic status, physical activity, smoking, other chronic conditions	Self-reported medical history	Underweight (<18.5): OR (95% CI) = 1.75 (0.63, 4.85) Normal weight (18.5–24.9): Ref. Overweight (25–29.9): 1.77 (1.30, 2.43) Obese (≥30): 3.01 (2.21, 4.08)
Han Y et al, 2021 (221), China	461,047 adults aged 30–79	Measured weight, height, and WC	Median follow-up of 11.2 years	Age, study areas, sex, education, marital status, family history of cardiometabolic disease, smoking, alcohol consumption, dietary habits, physical activity	Medical record	BMI <18.5 or ≥28.0 kg/m^2 or having WC ≥90 cm (men)/85 cm (women): HR (95% CI) = 1.63 (1.57, 1.68)

[a] BMI was calculated as weight (kg) divided by the squared height (m). BMI, body mass index; HR, hazard ratio; CI, confidence interval; OR, odds ratio; WC, waist circumference. Cardiometabolic multimorbidity was defined as at least two of defined as at least 2 of diabetes, coronary heart disease, and stroke.

11.3 Summary of studies investigating the associations between body mass index (BMI)/weight change and dementia.

Reference	Study population	BMI/weight change	Follow-up (years)	Dementia	Results
Buchman AS et al. 2005 (95), US	832 participants with mean age of 78.3 years from the Religious Orders Study	Annual rate of BMI change before incident dementia	5.6	Clinical examination	Per 1 kg/m^2/year increase: 0.71 (0.58-0.86)
Luchsinger JA et al. 2007 (172), US	4,536 participants aged ≥65 years in northern Manhattan	Annual rate of weight change over 3 years	5.1	Clinical examination	Stable weight (within 1 kg/y of loss or gain): Ref. Dementia: weight loss (>-1 kg/y): 1.9 (1.2-2.9) weight gain (>1 kg/y): 1.1 (0.7-1.9) Alzheimer Disease: weight loss: 1.3 (0.8-2.2) weight gain: 0.9 (0.5-1.8) Dementia associated with stroke: weight loss: 4.9 (1.9-12.9) weight gain: 2.8 (1.0-7.9)
Atti AR et al. 2008 (173), Sweden	1,255 participants aged ≥75 years from the Kungsholmen Project	BMI change over 3 years	Up to 6	Clinical examination and medical record	Decrease >10%: 1.58 (1.02-2.46) Decrease 5-10%: 0.92 (0.61-1.38) Stable ± 5%: Ref. Increase 5-10%: 0.94 (0.47-1.88) Increase >10%: 1.36 (0.62-3.00)
Power BD et al. 2013 (90), Australia	4,181 men aged 65–84 years, resident in Perth	BMI change over 6 years	5.9	Medical record	BMI loss (>1 unit): 1.89 (1.32-2.70) stable: reference BMI gain (>1 unit): 1.28 (0.82-2.01) BMI loss (>2 unit):1.66 (1.13-2.43) stable: reference BMI gain (>2 unit): 0.79 (0.40-1.54)

Reference	Study population	BMI/weight change	Follow-up (years)	Dementia	Results
Park S et al. 2019 (94), Korea	67,219 participants aged 60–79 years from the National Health Insurance Service-Health Screening Cohort	BMI change over 2 years	5.3	Medical record	Men: Decrease of >10%: 1.26 (1.08-1.46) Decrease of 5<−10%: 1.19 (1.09-1.29) Stable at ±5%: Ref. Increase of 5<−10%: 1.02 (0.92-1.12) Increase of >10%: 1.25 (1.08-1.45) Women: Decrease of >10%: 1.15 (1.03-1.29) Decrease of 5<−10%: 1.11 (1.03-1.19) Stable at ±5%: Ref. Increase of 5<−10%: 1.07 (0.99-1.15) Increase of >10%: 1.17 (1.05-1.31)
Eymundsdottir H et al. 2021 (92), Iceland	2,620 participants aged >60 years from the Age Gene/Environment Susceptibility-Reykjavik Study	Weight change over 5 years	5.2	Clinical examination	Weight loss ≥5%: odds ratio = 1.08 (95% CI 0.61-1.91) Stable ± 5%: Reference Weight gain≥5%: 2.70 (1.51-4.82)
Shen J et al. 2022 (96), US	5,985 participants aged ≥65 years from the Health and Retirement Study	Annual weight change	7.5	Medical record	Weight loss (lowest tertile): 1.57 (1.30-1.89) Stable weight (middle tertile): reference Weight gain (highest tertile): 0.92 (0.73-1.16)
Lu Y et al. 2022 (98), Japan	6,672 disability-free Japanese adults aged ≥65 years	Weight change over 12 years	5.7	Medical record	Weight loss ≥ -5.5 kg: 1.64 (1.29–2.09) -5.4 to -4.5 kg: 1.27 (0.92–1.77) -4.4 to -3.5 kg: 1.28 (0.91–1.81) -3.4 to -2.5 kg: 0.98 (0.70–1.38) -2.4 to -1.5 kg: 0.97 (0.70–1.34) Stable weight: Ref. Weight gain (≥ +1.5kg): 0.82 (0.63-1.06)

Effect size was presented as hazard ratio (95% confidence interval) unless specified.

11.4 Summary of studies concerning the associations of body mass index (BMI) with overall survival and survival free from chronic diseases.

Reference	Study population	BMI	Follow-up (years)	Outcomes	Results			
						Overall survival	Disease-free survival	Survival with disease
Pardo Silva MC et al. 2006 (167), US	2,551 adults free from CVD aged 45 years, from Framingham Heart Study.	Measured	Mean follow-up 32.0 years	Medical records and clinical examinations : CVD	Women Normal weight Overweight Obesity Men Normal weight Overweight Obesity	 Ref. -1.3 (-2.7, 0.3) -6.9 (-9.3, -5.0)* Ref. -0.9 (-2.4, 0.7) -3.3 (-5.5, -1.3)*	 Ref. -2.1 (-3.7, -0.4)* -8.4 (-10.8, -6.2)* Ref. -2.5 (-4.0, -0.7)* -6.0 (-8.1, -4.1)*	 Ref. 0.8 (-0.4, 2.1) 1.4 (-0.3, 3.2) Ref. 1.5 (0.3, 2.8)* 2.7 (1.0, 4.4)*
Nusselder WJ et al. 2009 (168), US	4,634 adults free from CVD age ≥50 years from Framingham Heart Study	Measured	Up to 12 years	Medical records and clinical examinations : CVD	Women Normal weight Overweight Obesity Men Normal weight Overweight Obesity	 1.0 (-0.2, 2.2) 1.7 (0.2, 2.3)* Ref. 1.3 (0.2, 2.5)* 1.6 (0.3, 3.1)* Ref.	 2.9 (1.6, 4.2)* 1.9 (0.3, 3.5)* Ref. 3.1 (1.9, 4.4)* 1.7 (0.2, 3.3)* Ref.	 -1.9 (-2.9, -1.0)* -0.2 (-1.5, 1.0) Ref. -1.8 (-2.8, -0.9)* -0.1 (-1.3, 1.1) Ref.
Dhana K et al. 2016 (124), Netherlands	6,499 adults free from diabetes aged ≥55 years from Rotterdam Study	Measured	Median follow-up of 11.1 y	Medical records and clinical examinations : diabetes	Women Normal weight (Ref.) Overweight Obesity Men Normal weight (Ref.) Overweight Obesity	 31.5 (31.1, 32.1) 32.4 (31.8, 33.1)* 32.2 (31.3, 33.0) 27.3 (26.7, 27.9) 26.9 (26.5, 27.5) 27.3 (26.0, 28.6)	 29.4 (28.4, 30.5) 27.4 (25.2, 29.6) 24.8 (21.1, 28.5)* 24.9 (24.1, 25.7) 23.4 (22.6, 24.4)* 22.1 (19.1, 24.7)*	 2.1 (1.3, 2.9) 5.1 (3.1, 6.7)* 7.4 (4.0, 10.8)* 2.4 (1.9, 3.0) 3.5 (2.8, 4.1)* 5.2 (3.1, 7.9)*
Dhana K et al. 2016 (127), Netherlands	6,636 adults free from CVD aged ≥55 years from the Rotterdam Study	Measured	Up to 12 years	Medical records: CVD	Women Normal weight (Ref.) Overweight Obesity Men Normal weight (Ref.) Overweight Obesity	 30.8 (30.3, 31.3) 31.3 (30.7, 32.0) 30.7 (30.0, 31.5) 26.5 (26.0, 27.1) 26.6 (26.1, 27.2) 26.8 (25.5, 28.1)	 27.1 (26.5, 27.7) 26.8 (26.0, 27.6) 25.2 (24.1, 26.1)* 22.3 (21.6, 23.0) 21.3 (20.7, 22.0) 19.7 (17.7, 21.7)*	 3.7 (3.2, 4.1) 4.5 (3.9, 5.2)* 5.3 (4.4, 6.3)* 4.2 (3.8, 4.7) 5.3 (4.8, 5.8)* 7.1 (5.4, 8.9)*

Reference	Study population	BMI	Follow-up (years)	Outcomes	Results			
						Overall survival	Disease-free survival	Survival with disease
O'Doherty, MG et al. 2016 (169), Denmark, Germany, Norway	1,759 from RCPH, 8,482 from ESTHER, 9,179 from Tromsø study, aged ≥50 free from CVD at baseline	Measured or self-reported	Mean follow-up range from 9 to 21 for different studies	Medical records: CVD	Women (normal weight as the Ref.)	Underweight had shorter but overweight and obesity had similar overall survival in RCPH and ESTHER; Underweight had a shorter but overweight had a longer overall survival in Tromsø.	Underweight had shorter CVD-free survival in all three cohort studies; Overweight had longer CVD-free survival in ESTHER.	Overweight and obesity had longer survival with CVD in Tromsø.
					Men (normal weight as the Ref.)	Underweight had shorter but overweight and obesity had similar overall survival in RCPH; Overweight had longer overall survival in ESTHER and Tromsø.	Underweight had shorter CVD-free survival in all three cohort studies; Overweight had longer CVD-free survival in ESTHER.	Overweight and obesity had longer survival with CVD in Tromsø.
Stenholm S et al. 2017 (126), England, Finland, France and Sweden	72,942 from the ELSA, FPS, SLOSH, and GAZEL study aged ≥50 free from chronic diseases	Self-reported		Self-reported diabetes, CVD, chronic lung disease, and cancer		Overweight had shorter disease-free survival in the FPS, GAZEL, SLOSH, but not in ELSA; Obesity had shorter disease-free survival than normal weight		
		Measured			Women			

Reference	Study population	BMI	Follow-up (years)	Outcomes	Results			
						Overall survival	Disease-free survival	Survival with disease
Khan SS et al. 2018 (54), US	91,320 participants free from CVD aged 60-79 from the Cardiovascular Disease Lifetime Risk Pooling Project		Median follow up of 11 years	Clinical examinations : CVD	Underweight (<18.5)	18.9*	17.0*	1.9
					Normal weight (Ref.)	22.4	20.4	2.0
					Overweight (25.0-29.9)	22.7	20.2	2.5*
					Obesity (30.0-39.9)	21.2	18.7*	2.5*
					Morbid obesity (≥40.0)	18.5*	16.2*	2.4*
					Men			
					Underweight	11.9*	10.9*	1.0*
					Normal weight (Ref.)	17.7	15.6	2.1
					Overweight	18.7	16.0	2.7*
					Obesity	17.9	15.3	2.6*
					Morbid obesity	15.3	12.0*	3.3
Nyberg ST et al. 2018 (128), Denmark, Finland, France, Sweden, UK	73,054 women (mean age 43.4), and 47,127 men (mean age 44.6) free from chronic diseases from the IPD-Work consortium	Measured or self-reported	Mean follow-up 11·5 years	Medical records or clinical examinations : diabetes, CVD, cancer, asthma, and chronic obstructive pulmonary disease	Women			
					Underweight		0.0 (-1.4, 1.4)	
					Normal weight		Ref.	
					Overweight		-1.1 (-1.5, -0.6)*	
					Class I obesity		-2.7 (-3.9, -1.5)*	
					Class II-III obesity		-7.3 (-8.6, -6.1)*	
					Men			
					Underweight		-1.8 (-4.9, 1.3)	
					Normal weight		Ref.	
					Overweight		-1.1 (-1.5, -0.7)*	
					Class I obesity		-3.9 (-4.9, -2.9)*	
					Class II-III obesity		-8.5 (-9.8, -7.1)*	
Li Y et al. 2020 (125), US	73,196 participants from the NHS and 38,366 participants from the HPFS free from cancer, CVD, and diabetes	Self-reported	Up to 34 years of follow-up in NHS and 28 years in the HPFS	Self-reported cancer (except non-melanoma skin cancer), CVD, and diabetes	Women	%LE free of chronic diseases/total LE at age 50 years		
					BMI <18.5		86.3	
					BMI 18.5-22.9		84.0	
					BMI 23-24.9		82.9	
					BMI 25-29.9		79.4	
					BMI 30-34.9		73.6	
					BMI ≥35		72.2	
					Men			
					BMI <18.5		74.3	
					BMI 18.5-22.9		79.8	
					BMI 23-24.9		78.8	

Reference	Study population	BMI	Follow-up (years)	Outcomes	Results			
						Overall survival	Disease-free survival	Survival with disease
					BMI 25-29.9		75.9	
					BMI 30-34.9		70.3	
					BMI ≥35		68.0	

CVD, cardiovascular disease; RCPH, Research Centre for Prevention and Health; ESTHER, Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung; ELSA, English Longitudinal Study of Ageing; FPS, Finnish Public Sector study; SLOSH, Swedish Longitudinal Occupational Survey of Health; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study ; IPD-Work, Individual-Participant-Data Meta-Analysis in Working Populations; LE, life expectancy.

BMI was categorized as underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), obesity (≥30.0; class I obesity, 30.0-34.9 and class II-III obesity, ≥35.0) unless specified. * The difference of survival between corresponding BMI group and normal weight was statistically significant (P <0.05).

11.5 Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991-2022

1991
Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992
Borell Lena. The activity life of persons with a dementia disease.

1993
Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.
Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.
Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994
Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)
Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.
Josephsson Staffan. Everyday activities as meeting-places in dementia.
Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.
Forsell Yvonne. Depression and dementia in the elderly.

1995
Mattiasson Anne-Cathrine. Autonomy in nursing home settings.
Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996
Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.
Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)
Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997
Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.
Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998
Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.
Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.
Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)
Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999
Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.
Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.
Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000
Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)
von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001
Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.
Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.
Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002
Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.
Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003
Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004
Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.
Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.
Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.
Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.
Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005
Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.
De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.
Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.
Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.
Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.
Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006
Klarin Inga. Drug use in the elderly – are quantity and quality compatible.
Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.
Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.
Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007
Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)
Westerbotn Margareta. Drug use among the very old living in ordinary households- Aspects on well-being, cognitive and functional ability.
Rehnman Jenny. The role of gender in face recognition. (Stockholm University)
Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?
Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008
Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)
Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.
Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.
Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.
Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)
Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.
Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009
Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.
Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.
Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.
Livner Åsa. Prospective and retrospective memory in normal and pathological aging.

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010
Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.
Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011
Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.
Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.
Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012
Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.
Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.
Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013
Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.
Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014
Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.
Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015
Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.
Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.
Svärd Joakim. Emotional facial processing in younger and older adults.
Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.
Pantzar Alexandra. Cognitive performance in old-age depression.

2016
Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.
Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.
Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.
Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.
Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017
Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.
Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.
Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.
Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018
Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.
Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.
Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.
Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.
Sjöberg Linnea. Using a life-course approach to better understand depression in older age.
Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

2019
Seblova Dominika. Causal effects of education on cognition – How do we generate evidence?
Berggren Rasmus. Cognitive development and educational attainment across the life span.

Vetrano Davide Liborio. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.
Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.
Pan Kuan-Yu. Impact of psychosocial working conditions on health in older age.
Avelar Pereira Bárbara. Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging
Morin Lucas. Too much, too late? Drug prescribing for older people near the end of life.
de Boer Lieke. Dopamine, decision-making, and aging: Neural and behavioural correlates.
Ek Stina. Predictors and consequences of injurious falls among older adults: A holistic Approach.
Ding Mozhu. The role of atrial fibrillation in cognitive aging: a population-based study

2020
Dintica Cristina Silvia. Oral health & olfactory function: what can they tell us about cognitive ageing?
Payton Nicola Maria. Understanding preclinical dementia: early detection of dementia through cognitive and biological markers.
Li Xin. The relation among aging, dopamine-regulating genes, and neurocognition.
Grande Giulia. Development of dementia in older adults: the body-mind connection.

2021
Shang Ying. How can older adults combat diabetes to achieve a longer and healthier life?
Sif Eyjólfsdóttir Harpa. Unequal tracks? Studies on work, retirement and health.
Sundberg Louise. Better all the time? Trends in health and longevity among older adults in Sweden.

2022
Saadeh Marguerita. Enjoying life and living healthier: impact of behavioral and psychosocial factors on physical function in old age.