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Obesity and common mental disorders: Examination of the association using alternative longitudinal models in the Whitehall II prospective cohort study

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Declaration of authorship

I, Markus Jokela, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Part of the results have been previously published in academic journals (Jokela M, ..., Kivimäki M. "Natural course of recurrent psychological distress in adulthood." *Journal of Affective Disorders* 2011, 130, 454-461; Kivimäki M, ..., Jokela M. "Common mental disorder and obesity: insight from four repeat measures over 19 years: prospective Whitehall II cohort study." *British Medical Journal* 2009, 339, b3765; Kivimäki M, ..., Jokela M. "Association between common mental disorder and obesity over the adult life course." *British Journal of Psychiatry* 2009, 195, 149-155). In these papers, I developed the statistical analysis protocol. The previously published results represent only a limited part of the broader multilevel framework developed for the present thesis, which is based on complete data from all available Whitehall II data phases unlike in the published papers. The methodological differences are described in more detail on page 65-66 of the Results section.

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Abstract

This thesis examined the bidirectional association between obesity and common mental disorders (CMDs) using alternative longitudinal models. Although previous evidence from different studies suggests that obesity increases the risk of CMDs and CMDs increase the risk of obesity, a more detailed longitudinal analysis is needed in order to better understand the temporal patterns.

The participants were from the Whitehall II prospective cohort study with 5 data collection waves between 1985 and 2009 (n=10,265 participants in total contributing 35,880 person-observations over the follow-up), aged 35 to 55 at baseline. Body mass index (BMI) was determined on the basis of height and weight measured in medical examinations, and CMDs were assessed with the self-reported General Health Questionnaire (GHQ). In addition, several covariates (occupational status, sleep duration, bodily pain, alcohol consumption, smoking, physical activity, longstanding illnesses) were included. Associations were examined using multilevel regression.

Obesity increased and the level of CMDs decreased with age. The development of both obesity and CMDs were characterized by cumulative developmental patterns, that is, the risk of future obesity (or CMDs) increased progressively with the number of times the person had been obese (or had CMDs) in previous study phases. Standard longitudinal regression models suggested that obesity was prospectively associated with future CMDs, whereas CMDs did not predict future risk of obesity. However, chronic CMDs increased the risk of obesity, so that only individuals with CMDs in several study phases over the follow-up phase had elevated risk of future obesity. Such cumulative pattern was not observed for chronic obesity in predicting future CMDs. Analysis of changes of BMI and CMDs over time indicated that a decrease in BMI was associated with a future decrease in CMDs, and an increase of CMDs was associated with future increase in BMI. An increase in BMI, however, was not associated with future change in CMDs, and a decrease in CMDs was not associated with a decrease in BMI, suggesting that the associations between changes in BMI and CMDs are dependent on the direction of change in the exposure. Except for bodily pain, the covariates had little if any effect on the associations between obesity and CMDs, and only age showed a consistent moderating effect such that the cross-sectional association and the association between CMDs and the future risk of obesity increased in magnitude with age.

The results from several alternative longitudinal models suggest that the bidirectional association between obesity and CMDs is likely to represent the effects of multiple mechanisms that exert their influence over different time periods. Standard longitudinal regression models with only two measurement times are not sufficient to capture such complicated temporal patterns.

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Abbreviations

AHEI	Alternative Healthy Eating Index
BMI	Body Mass Index
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CIS-R	Clinical Interview Schedule, Revised
CMD	Common Mental Disorder
GHQ	General Health Questionnaire
HADS	Hospital Anxiety and Depression Rating Scale
HPA	Hypothalamic-pituitary-adrenal
OR	Odds ratio
SES	Socioeconomic status
SF-36	Short Form Health Survey

Chapter 1. Background

1.1. Obesity as a public health concern

Obesity is defined as a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired.[1] The most common measure used to determine relative body weight is body mass index (BMI) which is calculated as body weight in kilograms divided by the square of body height in metres (kg/m²). Categorization of individuals into groups of underweight, normal weight, overweight, and obese is commonly done using the cut-off values provided by the World Health Organization.[1] For adults 18 years or older, underweight is defined as BMI below 18.5, normal weight between 18.5 and 24.9, overweight between 25 and 29.9, and obesity as BMI of 30 or higher. The cut-off value for obesity (BMI≥30kg/m²) was based primarily on the reported associations between BMI and mortality.[1] For individuals younger than 18 years, age- and sex-specific cut-off values for overweight and obesity are used.[2]

Extensive research literature has confirmed the conjecture of Hippocrates dating back to 400 BC that "corpulence is not only a disease itself, but a harbinger of others." Obesity increases the risk of various medical conditions,[3-5] including type 2 diabetes,[6-8] cardiovascular diseases,[9,10] hypertension,[11] dyslipidemia,[12] respiratory diseases,[13,14] and some cancers,[15,16] and is one of the components of the metabolic syndrome.[17] Recent research has shown that obesity may also be accompanied by various health risks in domains other than the well-known cardiovascular and related chronic diseases, including cognitive impairments,[18] dementia[19,20] and Alzheimer's disease,[21] indicating that obesity is associated with a wide range of adverse health effects. Obese individuals may also have physical limitations interfering with normal activities of daily living, such as climbing stairs or

carrying groceries.[22-25]

The ultimate consequence of the health risks associated with obesity is premature mortality as demonstrated in several studies.[23,26-31] A collaborative analysis of 57 cohort studies and >900,000 participants suggested that obesity increases premature mortality risk by 30% compared to normal weight.[29] It has been argued that the increasing prevalence of obesity (see below) and the associated premature mortality may begin to adversely affect population life expectancy.[32-35] For example, Olshansky and colleagues[32] estimated that the current prevalence of obesity has already cut 0.3-1.1 years from the population life expectancy in the United States.

Obesity has become increasingly common in many countries over the last decades, which is why obesity is widely considered to be one of the most serious global health problems.[1,3,36-43] Although obesity is sometimes seen in the public arena as a "disease of affluence" assumed to affect mostly modern Western societies characterized by sedentary lifestyles and excessive food consumption, the obesity epidemic is not restricted to developed countries.[41] According to the statistics of the World Health Organization,[1,44] sub-Saharan Africa is the only region in the world where the prevalence of obesity has not increased in recent decades, although the rates of obesity in developing countries and certain parts of the world, Asia and Africa in particular, are considerably lower than in Europe and United States.[44]

Between 1980 and 2002 the prevalence of obesity in Britain increased three-fold, with 23% of men and 25% of women being obese at the beginning of the 21th century.[45] In Europe, the proportion of obese people varies between 4.0% and 28.3% in men and between 6.2% and 36.5% in women,[46] suggesting substantial variation between countries. Britain has the third-highest obesity prevalence in Europe, after Greece and Malta[44] but still has lower obesity prevalence than the United States where one-third of adults (34%) are obese.[47] Assuming that the future development of obesity in the United States continued at the same

rate as to date, it has been estimated that all Americans would be overweight or obese by year 2048.[48,48] However, most recent data suggests that the increasing obesity trend in the United States might be levelling off or at least slowing down.[40,47] Evidence of such a decelerating trend has not yet been reported for any European country.

The public health relevance of obesity has clearly increased over the recent decades, and it is gaining increasingly more attention. Empirical data demonstrating the physical health risks related to obesity date back already to the early 20th century. In the United States in the 1920's, the Metropolitan Life Insurance Company began to charge higher insurance rates for overweight than normal-weight individuals because the company's actuarial data showed elevated mortality risks in the overweight.[49] The issue of obesity and the public health was first brought up in modern epidemiological context by Lester Breslow who, in a brief paper published in 1952,[49,50] drew attention to the health consequences of the increasing prevalence of overweight in the United States - at a time when obesity was still rare by modern standards. Already at that time the paper predicted that obesity was becoming an increasingly relevant factor in determining population health.

1.2. Common mental disorders as a public health concern

Depressive and anxiety disorders are considered to be among the most detrimental mental health problems affecting large numbers of community-dwelling individuals.[51-55] There is substantial comorbidity between disorders of depression and anxiety; 50%-60% of individuals with a life-time history of major depression also have a lifetime history of at least one anxiety disorder.[56] Accordingly, self-reported mental health problems in general populations and community samples are often characterized by co-morbidity between symptoms of depressive episodes, neurotic disorders and stress-related disorders.[57-60] While clinical interviews and diagnostic criteria can be used to discriminate between symptoms of

depressive and anxiety disorder in psychiatric practice, self-reported symptoms are often too heterogeneous to be reliably measured by specific subscales of depression and anxiety due to the considerable overlap between them. In other words, most of the variance in self-reported measures of depression, anxiety, and stress-related symptoms reflects a single underlying factor of general psychological distress.[61-67]

The concept 'common mental disorders' (CMDs) refers to symptoms of psychological distress that cause emotional disturbance and significant impairment in daily living.[60,68] The core components of CMDs are symptoms of depression (low mood, loss of interest, inability to enjoy normal activities), anxiety (excessive worry, panic, phobias), and stress (inability to concentrate, irritability, sleep problems, somatic symptoms, fatigue). CMDs can be assessed using psychiatric interviews (e.g., the revised Clinical interview Schedule, CIS-R) or self-administered screening instruments, such as the General Health Questionnaire (GHQ;[58]).

In the general population, CMDs are considerably more common than major psychiatric disorders, increasing their relevance to public health. The prevalence estimates for CMDs vary depending on the cut-offs used to define clinically significant CMD. In the 2007 British Psychiatric Morbidity Study[68] CMDs were assessed with the CIS-R interview. Clinically significant CMD was defined as a score of 12 or more on a scale from 0 to 49, a score between 12 and 17 indicating clinically significant CMD unlikely to need treatment and a score of 18 or more indicating severe CMD requiring treatment. 12% of men and 18% of women suffered from CMDs, and approximately half of these cases were evaluated to be in need of treatment for mental health (6% in men, 9% in women). Based on commonly used cut-off values for the GHQ (a score of 3+ with the 12-item GHQ or 5+ with the 30-item GHQ), the prevalence of CMDs is often estimated to be higher, around 25% in the British population.[69,70]

Although CMDs may not always be severe enough to meet clinical significance requirements in terms of psychiatric diagnosis, even minor CMDs have been shown to be associated with important health consequences. Mixed depression-anxiety disorder is

estimated to cause one fifth of days lost from work in Britain,[53] and symptoms of CMDs have been associated with problems in social relationships,[71] increased risk of medical illnesses such as coronary heart disease,[72-75] performance difficulties in everyday life,[60] and elevated risk of premature mortality.[76,77] Subclinical symptoms of CMDs increase the risk of developing a clinically diagnosable psychiatric disorder in the future.[60,78,79] Thus, CMDs are important indicators of mental health status because they cause psychological and functional impairments and because they predispose individuals to develop more severe psychiatric problems.

1.3. Link between obesity and common mental disorders

Given the public health importance of both obesity and CMDs, understanding the nature of the relationship between these two conditions is crucial and could potentially inform prevention and treatment of both obesity and CMDs. Although research interest in the mental health implications of obesity has emerged much later than interest in the medical risks associated with obesity,[80] a number of studies in the health psychology and public health literature have examined the topic, with increasing interest over the last two decades.

Body height and weight, as well as some measures of mental health, are almost routinely assessed in health surveys, so cross-sectional data on the association between obesity and various mental health indicators from these surveys are plentiful. de Wit et al.[81] estimated the pooled effect size of the obesity-depression association, derived from 17 studies and 204,507 participants, to be OR=1.18 (CI=1.10-1.37, p=0.04) when including all the studies and OR=1.26 (CI=1.17-1.36, p<0.001) when excluding two studies considered to be outliers. Five studies had carried out the analysis with men and women combined, and 3 of these reported a significant positive association between obesity and depression. Of the 11

studies examining the association separately by sex, 8 reported a significant positive association in women, and 3 reported a significant positive association in men. The association appeared to be stronger in women (OR=1.31, CI=1.27-1.40) than in men (OR=1.12, CI=0.96-1.30), although the statistical significance of the sex difference was marginal (p=0.06). In almost all the studies included in the meta-analysis, confidence intervals for the odds ratios were larger for men than for women, possibly reflecting lower number of men in the samples or lower prevalence of depression in men leading into greater measurement imprecision. In addition, the meta-analysis demonstrated more heterogeneity between studies among men than among women, suggesting that the obesity-depression association in men may be more contingent on modifying factors than that in women.[81] The meta-analysis was unable to give more detailed clues on the potential factors accounting for the heterogeneity in men.

Atlantis and Baker[82] reviewed 20 cross-sectional studies, and concluded that studies from the United States often find significant associations between obesity and depression, particularly in women, while studies from other countries are less conclusive. In the World Mental Health Survey of 62,277 adults from 13 countries,[83,84] obesity was associated with a modestly higher risk of depression (assessed with the Composite International Diagnostic Interview, CIDI 3.0) with an overall OR=1.1 (CI=1.0-1.3), although the association was not statistically significant in many of the countries when assessed separately.

Gariepy et al.[85] report a meta-analysis of obesity and anxiety disorders in 2 prospective studies and 14 cross-sectional studies. There is some overlap in the included studies between their meta-analysis and those of de Wit et al.[81] and Atlantis & Baker[82] because some of the studies included more than one measure of CMDs. In Gariepy's meta-analysis, the cross-sectional data suggested a heightened risk of anxiety disorders in obese individuals (OR=1.40, CI=1.23-1.57), with no differences between women and men.

Friedman and Brownell[80] provide a historical review of research examining the

psychological correlates of obesity. They divide the research program into three "generations" of studies, all reflecting somewhat different approaches to the issue. According to the authors, the first generation of studies was interested in identifying psychological differences between obese and non-obese individuals. These studies were primarily based on small-scale case-control designs that compared obese with non-obese participants. The second generation of studies began to explore risk factors for mental health problems within obese individuals. The purpose of these studies was to identify factors placing obese individuals at risk of psychological problems and thereby explaining why some obese individuals suffer negative psychological consequences whereas others do not. Importantly, both the first- and second-generation studies were based mainly on cross-sectional designs. The studies reviewed by de Wit et al.[81] and by Atlantis and Baker[82] mainly illustrate these early-generation studies of obesity and mental health.

In the 1995 review of Friedman and Brownell,[80] the authors envisioned a third generation of studies extending earlier research on obesity and depression. The aim of these studies was to establish causal links between obesity, depression, and other risk factors related to the two. Because most of the evidence at the time was based cross-sectional, the authors concluded that "it is apparent from this discussion that little information exists on the presence or absence of causal relationships between obesity and psychopathology" [80] (p. 16). During the 16 years since the publication of Friedman and Brownell's review, there have been an increasing number of longitudinal studies examining the association between obesity and CMDs. Longitudinal studies cannot yet establish causal associations with the same degree of certainty as randomized controlled trials, but the presence or absence of specific longitudinal associations should provide a better understanding of how obesity and CMDs may be associated with each other over time.

The two following chapters review prospective studies of obesity and CMDs examining whether obesity predicts later risk of CMDs (Chapter 2) and whether CMDs predict later

obesity risk (Chapter 3). Current evidence suggests that the psychological correlates of obesity are not specific to depression or anxiety but extend to general psychological distress,[86,87] so the associations should not be strongly dependent on the measure of CMDs used in the study. Therefore, the following reviews of prospective studies include all available research reports irrespective of the specific measure of CMDs. Both chapters also briefly review the plausible mechanisms suggested to explain the influence of obesity on the development of CMDs, and vice versa. Some but not all of these mechanisms are examined empirically in the present thesis.

Following Chapters 2 and 3 reviewing the prospective studies of obesity and symptoms of CMDs, Chapter 4 considers factors that may modify the bidirectional associations between obesity and CMDs. As described above, the idea that obesity may be associated with detrimental mental health consequences only in some obese individuals has already been explored in the early studies of the psychological correlates of obesity.[80] The meta-analysis of de Wit[81] found substantial heterogeneity between studies of obesity and depression, particularly in men, suggesting that the associations may vary in strength between specific subpopulations. Stratifying individuals according to such moderating factors may help to explain some of the inconsistent findings arising from previous literature. Chapter 4 concentrates six factors, age, sex, socioeconomic status, chronicity of obesity/CMD, and time-period effects, as the most promising candidates for potential moderator variables.

Chapter 2. Obesity as a cause of common mental disorders – Literature review of previous studies and plausible mechanisms

2.1. Prospective studies of obesity and common mental disorders

Three prospective studies from the Alameda County Study, a prestigious cohort study in the United States, have explored the association between obesity and new onset of depression among adults of 50 years or older with no previous history of depression (n=1739 to 2298) using 1-year[88] and 5-year[89,90] follow-up periods. Depression was assessed using self-reported depression symptom inventory adapted from the PRIME-MD checklist. In the first study with a 1-year follow-up,[88] obesity was associated with an increased risk of depression incidence (OR=1.73; CI=1.04, 2.87). This result was replicated in the two later studies with 5-year follow-ups,[89,90] so that obesity increased the risk of incident depression by OR=1.79 (CI=1.06, 3.02) and by OR=1.48 (CI=0.96, 2.28). Although from the same study with the same follow-up, the difference between the two latter estimates reflects the differences in the set of covariates adjusted in the analysis. Both studies controlled for age, gender, education, marital status, social support and negative life events, but only the latter association was additionally adjusted for chronic medical conditions, difficulties with usual activities of living, physical activity, and financial strain.[88] Given that the studies examined only new cases of depression, the findings provide evidence for obesity being associated with increased risk of incident depression.

The Northern Finland 1966 Birth Cohort Study[91] explored the association between adolescent obesity assessed at age 14 and depressive symptoms (Hopkins Symptom Checklist-25 questionnaire) assessed 17 years later at age 31 (n=8451). Obese adolescents had a higher risk of exhibiting depressive symptoms as adults. This association was somewhat stronger in men (OR=1.97; CI=1.06, 3.68) than in women (OR=1.55; CI=0.93, 2.59). However, as depressive symptoms were not assessed at baseline, it was not possible to exclude alternative explanations, such as childhood or adolescent depressive symptoms increasing adolescent obesity rather than adolescent obesity increasing the risk of later depression.

To date, the largest study to examine the prospective association of obesity with later CMDs is probably the Nord-Trondelag Health Study (HUNT) with 44396 participants and an approximately 10-year follow-up period between 1985-6 and 1995-7.[92] Height and weight were measured in a medical exam and depressive symptoms at follow-up were self-reported with the 14-item Hospital Anxiety and Depression Rating Scale (HADS). Of the 14 questions of HADS, 4 were also included in the baseline questionnaire, which allowed the researchers to adjust for baseline symptoms assessed with the brief version of the HADS. In models adjusted for baseline HADS, sociodemographic factors, and health behaviors, baseline obesity predicted increased risk of depression in the total cohort (OR=1.29, 1.14-1.45). This association was slightly stronger in men (OR=1.41, 1.17-1.70) than in women (OR=1.21, 1.03-1.41). Obesity also predicted symptoms of anxiety in the total cohort (OR=1.16, 1.03-1.31) and in men (OR=1.50, 1.23-1.83) but not in women (OR=0.99, 0.85-1.15).

Goodman and Whitaker[93] examined the obesity-depression association in a sample of 9374 U.S. adolescents participating in the National Longitudinal Survey of Youth. Depressive symptoms were assessed with the CES-D self-report questionnaire. BMI was calculated from self-reported body weight and height. Over a 1-year follow-up, obesity did not significantly increase the risk of incident depression when baseline obesity was controlled for (OR=1.16, 0.81-1.65). Needham et al.[94] applied latent growth curve modeling

in a sample of 4643 American young adults with repeated measurements of depressive symptoms. They observed no association between baseline BMI and later development of depressive symptoms over 20 years of follow-up. In the 1946 British birth cohort,[95] trajectories of BMI from adolescence to adulthood were not associated with adult-onset depressive symptoms, providing no evidence for the temporal order from high BMI to elevated risk of depression later in life. In a sample of elderly Americans with a mean age 72 years (n=3981) followed for 3 years,[96] there was an increased risk of depression associated with obesity (OR=1.76) but this relationship was too imprecisely estimated to be reliable (CI=0.47-6.57).

Taking a slightly different approach than used in most studies, Gariepy et al.[97] examined both the prevalence and incidence of major depression in 10,545 Canadians participating in the National Population Health Survey. Obese individuals were approximately 1 percentage point more likely to be depressed in 6 of the 7 follow-up phases of their study (approximately 5% in obese vs. 4% in non-obese; see figure 1 in Gariepy et al.,[97] exact odds ratios not reported in the article). However, when examining the incidence rather than prevalence of major depression with survival analysis, obesity was associated with a lower risk of incident depression in men (HR=0.71, CI=0.51-0.98) whereas no association was observed in women (HR=1.03, CI=0.84-1.26). This pattern suggests that the positive association between obesity and prevalence of depression may reflect a separate phenomenon to the effect of obesity on depression incidence, perhaps mediated by different mechanisms.

In addition to the large studies reviewed above, several smaller studies (n<1000) have investigated the longitudinal association of obesity with CMDs. In a sample of 674 American adolescents followed for 20 years, Anderson et al.[98] observed obesity to be associated with a heightened risk for clinical depression in adulthood, OR=2.00 (CI=1.00-4.01, p=0.05). In the Great Smoky Mountain Study of 991 children and adolescents

aged 9 to 16 years, Mustillo et al.[99] examined how age-related growth trajectories of BMI were associated with the development of psychiatric disorders, including depression and anxiety, over a follow-up period of 8 years. Boys with chronic obesity (obesity at both of the two assessment times) were more likely than other boys to develop depressive disorder by the end of the follow-up period, while no association was observed in girls.

In 544 mothers participating in the Children in the Community Study,[100] obesity at age 27 predicted increased odds of major depressive disorder (OR=3.96, 1.23-12.74) and generalized anxiety disorder (OR=4.49, 1.21-16.69). Adjusting for race/ethnicity, education, financial situation, marital status, chronic diseases, social support, and baseline depressive symptoms strengthened these associations to OR=5.25 (1.41-19.58) and OR=6.27 (1.39-28.16), indicating a strong but imprecisely estimated association between baseline obesity and symptoms of depression and anxiety assessed 22 years later. In a Finnish study[101] of metabolic syndrome and depressive symptoms in adults (n=688, 7-year follow-up), obese individuals not depressed at baseline were more likely to have depressive symptoms at follow-up compared to those with normal weight (22% vs. 14%), although this difference was did not reach statistical significance at conventional levels (p=0.09). Waist circumference was also positively but non-significantly associated with depressive symptoms in men (OR=1.3, 0.5-3.5) and women (OR=1.4, 0.7-2.8). The Maastricht Aging Study[102] followed 1169 adults and examined whether overweight (or continuously measured BMI) at baseline predicted depressive symptoms assessed with the CES-D after 6 years of follow-up. Overweight individuals had higher depression score at follow-up (mean=8.6, SD=7.0 vs. mean=7.5, SD=6.4) but the association between overweight and depression risk was not significant in a model adjusted for health behaviors (smoking, alcohol consumption, physical activity), OR=1.11 (0.75-1.61).

Luppino et al.[103] performed a meta-analysis with 15 prospective studies that assessed the bidirectional association between obesity and depression. Of the 8 studies used to obtain

a pooled estimate of baseline obesity in predicting future depression risk, 5 reported a statistically significant positive association between obesity and depression. The overall estimate suggested that obesity at baseline increases the odds of later depression by 55% (22% to 98%). The association was slightly but not significantly stronger in studies with more than 10-year follow-up compared to studies with less than 10-year follow-up (OR=1.72 vs. OR=1.26; p for difference p=0.24), and when depression was assessed with clinical interview compared to self-reported depressive symptoms (OR=2.15 vs. OR=1.36; p=0.05). Studies in the United States produced stronger associations than studies in European countries (OR=2.12 vs. OR=1.33; p=0.05). There was also some suggestion of a stronger association in samples with mean age above 60 years compared to studies with mean age between 20 and 59 but this difference was not significant (OR=1.98 vs. OR=1.34; p=0.52). There was no significant sex difference in these associations (OR=1.31 in men, OR=1.67 in women; p=0.81).

2.2. Plausible mechanisms

Several mechanisms possibly explaining the association between obesity and increased risk of CMDs have been suggested, including limited physical functioning and pain, stigma and discrimination, and negative self-image.

2.2.1. Limited physical functioning and bodily pain

Obesity tends to induce physical and functional limitations in daily life.[22,25,104] Obesity also increases the risk of developing disabling bodily pain, particularly in the knee joints.[105-107] Accordingly, obese people report worse health-related quality of life than normal weigh people.[108-110] Functional impairment and bodily pain, in turn, are known to increase the risk of depressive symptoms,[111] so it is plausible that functional limitations and bodily pain in part explain the influence of obesity on the development of CMDs.

2.2.2. Stigma and discrimination

A number of studies have shown that obesity is perceived negatively, or stigmatized, in many contemporary societies, and that most people have negative attitudes about obesity.[112-116] These attitudes are internalized from early on. In a study of obesity stereotypes, 3-year-old children rated "chubby" target figures more negatively than otherwise similar figures that were thin or average weight.[117] In another study, 6-year-old children rated silhouettes of overweight children more negatively than normal-weight silhouettes.[118] Similar findings have been obtained in studies of adolescents and adults, including people who are obese themselves.[119-122] Medical professionals also tend to have negative attitudes toward obese individuals.[123] The negative connotations related to obese individuals appear to be "contagious". In an experimental study, male job applicants were rated less favourably if they had been seen in the company of an obese woman than if they had been seen to interact with an average-weight woman, regardless of whether the subjects rating the applicants thought that the obese woman was a stranger or a romantic partner of the applicant.[124]

Owing to the average "anti-obesity" attitudes and perceptions, obese people are more likely than non-obese to face bullying, discrimination, and mistreatment from strangers, acquaintances, and intimates.[113,115,116] In the National Survey of Midlife Development in the United States (MIDUS) study,[125,126] obese individuals were more likely than normal-weight individuals to report having been rudely treated by strangers, acquaintances, and professionals with whom they had interacted. In employment settings, obese individuals are less likely than non-obese individuals to be selected for a job or getting promoted, and more likely to be discharged and disciplined.[127] Overweight children have been shown to receive less financial support for college from their parents than normal-weight children even when controlling for parental and child characteristics potentially confounding the association,

such as parental income, ethnicity, family size, and child's grades.[116] Such adverse effects appear to be less severe in subcultures and societies where obesity is less stigmatised, e.g., in certain ethnic groups.[115,119,121] In sum, discrimination and stigmatization of obesity can become expressed in various ways in the daily life of obese people, and the cumulative effect of such experiences may increase the risk of mental health problems, potentially explaining why obesity predicts CMDs.

2.2.3. Negative self-image and health perceptions

The social stigma and discrimination discussed above reflect the reactions and behaviors of other people, and their influence on the mental wellbeing of obese vs. non-obese individuals. Explanations of the obesity-depression association have also emphasized the role of obese individuals' own perceptions of themselves.[80,122,128,129] Overweight and obese people tend to be less satisfied with their body size and shape,[128] and internalization of a negative self-body image and obesity stereotypes may predispose to the development of depression.[128,129] The body image hypothesis is strengthened by studies demonstrating that such self-related perceptions may increase the risk of psychological distress regardless of actual body weight.[130] In a cross-sectional study of Australian adults, persons who perceived themselves as overweight had higher psychological distress than those who considered their body weight to be within acceptable range, even when actual body weight was adjusted for.[130] Weight perception itself was a more important predictor of psychological distress than weight misperception, i.e., the discrepancy between perceived and actual weight. The authors of the study suggested that people's perceptions of their weight status may induce a positive correlation between obesity and psychological distress.

Some researchers have suggested that weight perceptions may not only contribute to negative body image but also affect subjective perceptions of poor health more generally.[86,131] Obese individuals who perceive their general physical health to be poor, e.g., because of the

functional limitations they encounter in daily life or the knowledge of medical illnesses associated with obesity, may develop more generalized beliefs of ill health that adversely affect their mental health. For instance, people with excessive body weight may believe that they are unable to engage in certain occupations or leisure activities, or that they will not be able to have a long and fulfilling life, because of their obesity. Such perceptions of limitations and constraints may trigger depressive symptoms and beliefs.[86] Some researchers have argued that the recent media coverage of the obesity epidemic portraying obesity as a serious health concern for individuals may perpetuate an assumption that being obese is dangerous and unhealthy in many respects.[86] Internalization of such ideas of poor health may not necessarily encouraged to better weight control, but can negatively affect obese people's self-image and thereby increase the risk of CMDs.

Another proposed mechanism related to self-perceptions of obese individuals concerns weight loss or control. Obese individuals are more likely than normal-weight individuals to diet in order to lose their weight.[132] However, dieting rarely results in permanent decreases of body weight as most dieters tend to regain their weight soon after they stop dieting.[133] Repeated dieting attempts, dieting failures, and subsequent weight cycling, may increase levels of psychological distress by making individuals feel like failures.[134] Most people's memories of dieting tend to be negative,[135] and failures to uphold the diet also induce negative emotions.[136] Furthermore, being on a diet may itself increase psychological distress, because very low-calorie diets have been associated with irritability.[137] Caloric restriction may be particularly harmful to individuals vulnerable to depression, as evidenced by a study showing impaired regulation of brain serotonin functioning in response to dieting among women with a history of depression.[138] Thus, failed attempts to lose weight may result in heightened psychological distress and negative perceptions of the self, which in turn may increase the risk of developing CMDs.[134]

Chapter 3. Common mental disorders as a cause of obesity – Literature review of previous studies and plausible mechanisms

3.1. Prospective studies of common mental disorders and later obesity or weight change

At least four large-scale studies (n>1000) have examined whether depression predicts later risk of obesity. A study of 1037 adolescents living in New Zealand,[139,140] assessed whether depression measured in early (ages 11, 13, and 15) and late adolescence (ages 18 and 21) predicted the risk of obesity at age 26. Body height and weight were measured in a medical examination, and depression was diagnosed based on the Diagnostic Interview Schedule. Adjusted for baseline obesity, depression in early adolescence was not associated with adult obesity risk in either sex (OR=0.50, 0.19-1.28). In contrast, depression in late adolescence was associated with heightened risk of adult obesity in women (OR=2.32, 1.29-3.83) but not in men (OR=0.90, 0.37-2.02). In the Alameda County Study[89] introduced in the previous chapter, obesity was associated with later depression but depression at baseline did not predict obesity risk over a 5-year follow-up period when obesity at baseline was adjusted for (OR=1.32, 0.65-2.69). In a sample of 9374 adolescents from the U.S. Add Health study, depressed mood at baseline (measured with the CES-D self-report inventory) was associated with an 2.05-fold (1.18-3.56) increased odds of obesity when adjusted for baseline BMI.[93]

In the University of North Carolina Alumni Heart Study (n=4726; 82% men), symptoms of depression were assessed measured using the self-administered depression subscale of

the MMPI (Minnesota Multiphasic Personality Inventory) at the mean age of 18 years, and body weight and height were measured in a medical examination after 20 years of follow-up.[141] There was a complex interaction effect between baseline depression and BMI in predicting subsequent weight gain. Depressed participants who were initially lean gained less weight than lean participants who were not depressed. Conversely, depressed participants who were initially heavy gained more weight than heavy participants who were not depressed. In other words, depression strengthened the baseline differences in weight status.[141]

In the Zurich Cohort Study[142-144] of 591 participants aged 19 at baseline and followed for 20 years, high depression scores on the Symptom Checklist 90-R at age 19 increased the risk of adult obesity in women (baseline BMI adjusted HR=11.52, SE=1.24 in a proportional hazards model predicting the crossing the obesity threshold at follow-up phases) but not in men (HR=1.10, SE=0.66). Despite the absence of association for obesity in men, baseline depression was associated with a more rapid weight gain over time in both men and women.[143,144]

In a sample of 800 Swedish women aged 38 to 54 years,[145] higher scores of baseline HAM-D depressive symptoms were associated with greater weight gain over a period of 6 years (more than 5kg vs. less than 5kg weight gain). By contrast, in the U.S. National Health and Nutrition Examination Survey,[146] having a high depressive symptoms score assessed with the CES-D inventory was associated with 3kg greater weight gain in men compared to non-depressed men, but modestly reduced weight gain in women in a sample of adults less than 55 years of age. However, among women and men aged over 55 years, who on average lost rather than gained weight over the follow-up period, baseline depression was associated with additional weight loss.

Several studies have examined whether the associations between body weight and depression are observed already in childhood or adolescence, or whether the associations

emerge only in adulthood. A study of 644 American adolescents examined the association of adolescent depression measured at baseline (average age 14 years) in a clinical interview with obesity measured on the basis of self-reported data on body weight and height 9 years later.[147] Adolescent depression was associated with higher odds of obesity at an average age of 22 in the total sample (OR=1.75, 1.23-2.49). The association was stronger in women (OR=3.06, 1.91-4.91) than in men (OR=1.46, 0.78-2.74). Baseline depressive symptoms predicted greater BMI increase over the 9-year follow-up period into adulthood, but the effect was relatively modest and was lost when adjusted for covariates. In a smaller study[148] of sex-matched groups of children and adolescents aged 6-17 years with major depression (n = 90) vs. those with no psychiatric disorders (n = 87), the participants diagnosed with major depression had significantly higher BMI in young adulthood 10-15 years after baseline than those with no diagnosed depression (mean BMIs of 26.1 vs. 24.2, respectively).

At least one study has investigated the determinants of weight gain in a group of 6-12-year-old children who were at a risk for developing obesity due to being overweight or having an obese parent.[149] In these children, depressive symptoms (assessed with the Children's Depression Inventory) were unrelated to weight gain over a four-year follow-up. In a sample of American adolescent girls,[150] severe depressive symptoms (assessed with the Expanded Form of the Positive and Negative Affect Schedule) predicted an increased risk of obesity onset over a 4-year follow-up period with an unadjusted OR=4.62 (1.67-12.74) and an adjusted OR=2.32 (0.62-8.65) in a model including dietary patterns and parental obesity.

In the meta-analysis of Luppino et al.[103] cited in Chapter 2, 4 of the 9 included studies assessing the prospective association between baseline depression and subsequent risk of obesity reported a positive association. The overall odds ratios pooling the results of the 9 studies together indicated a 58% increased odds of obesity associated with depression (CI=33% to 87%). The association was stronger but not significantly so in women (OR=2.01, 1.11-3.65) than in men (OR=1.43, 0.96-2.13), p=0.50 for sex difference. No substantial

modifying effect was observed for duration of follow-up (OR=1.43, 1.13-1.81 for studies with shorter than 10-year follow-up; OR=1.76, 1.35-2.25 for studies with longer than 10-year follow-up), method of depression diagnosis (clinical assessment OR=1.71, 1.33-2.19; self-reported symptoms OR=1.48, 1.17-1.87), age at baseline (odds ratios in age groups of <20, 20-60, 60+ between OR=1.27 OR=1.76) or country of origin (OR=1.49, 0.97-2.28 for European studies; OR=1.61, 1.29-2.01 for American studies).

A meta-analysis by Blaine[151] pooling together data from studies examining the prospective association between depression and subsequent risk of obesity or weight gain included 17 studies, of which 11 reported a positive association. The pooled estimate, OR=1.19 (1.14-1.24), showed no significant sex difference (OR=1.34, 1.14-1.58 in men; OR=1.26, 1.20-1.32 in women). However, in contrast to the meta-analysis of Luppino et al.,[103] the association of depression with later obesity risk or weight gain was stronger in adolescent samples than in adult samples (OR=2.31, 2.06-2.58 vs. OR=1.08, 1.03-1.13). A strong association between adolescent depression and subsequent risk of overweight was also described by a narrative literature review of Liem et al.,[152] in which the results of 4 longitudinal studies meeting the quality criteria of the review[93,148,149,153] indicated a heightened risk, OR=1.9 to OR=3.5, of overweight associated with adolescent depression.

3.2. Plausible mechanisms

As in the case of obesity influencing the risk of CMDs, a number of explanations for the influence of CMDs on weight gain and the development of obesity have been proposed, but the empirical evidence for these mechanisms remains scarce. This section reviews the most prominent mechanisms suggested to account for the influence of CMDs on increased obesity risk. These include psychosocial stress; poor health behaviors, especially dysfunctional eat-

ing patterns and decreased physical activity; low self-efficacy and social support; and obesogenic side-effects of antidepressant medications.

3.2.1. Psychosocial stress

Psychosocial stress is thought to be a central risk factor in the onset of depression.[154-157] Negative life events, including unemployment, illness, divorce, or loss of a significant other,[158-161] and the lack of psychological and social resources to cope with such adverse circumstances,[162-166] have been shown to often precede the onset of a depressive episode. Stressful experiences in childhood and adolescence can also predispose to the development of depression in adulthood.[167,168]

Psychosocial stress has also been implicated as a risk factor for weight gain and obesity.[169-172] This association might be mediated by both behavioral and physiological mechanisms. Behaviourally, stress may adversely affect health behaviours that increase the risk of obesity, e.g., by making individuals eat more unhealthy snack food for comfort[173-176] and decrease levels of physical activity.[177,178] Physiologically, stress involves metabolic changes that may enhance the rate of energy reservation in fat cells.[170] A repeated and chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis indexed by increased secretion of cortisol has been suggested to increase fat accumulation and the risk of abdominal obesity.[170,179-183]

The development of obesity and depression may share a common neuroendocrine basis,[184,185] as depression is characterized by dysfunctional HPA axis activation and related neuroendocrine mechanisms underlying the stress response,[186-189] such as chronically elevated cortisol levels. These neuroendocrine correlates of depression are often manifested as elevated reactivity to stress.[187,190] Failure to regulate the HPA response appears to elevate the risk of relapse among clinically depressed patients.[187] It has been suggested that antidepressants may exert their beneficial effects on mental health via regulation and

normalization of the HPA response in stressful circumstances.[190] Given that these physiological pathways have also been demonstrated to modulate the rate of energy reservation and fat accumulation,[170] it is possible that depression increases obesity risk via a common underlying physiological mechanism.[184,185] There is some evidence of abnormal HPA axis hormone concentrations among obese people with and without co-existing depressive symptoms, and among obese people with binge eating disorder.[184,185]

3.2.2. Unhealthy behaviours

Whether related to psychosocial stress discussed above, or not, various health behaviors have been suggested to mediate the influence of CMDs on obesity risk. People with CMDs are more likely than their CMD-free counterparts to be physically inactive[93,177,178,191,192] which, in turn, increases the risk of developing obesity.[193-195] Increased alcohol consumption and smoking may also help to explain why CMDs would increase obesity risk, as some individuals suffering from CMDs may try to cope with the nervousness and stress with the help of alcohol[196] or smoking.[197]

Adverse dietary patterns contributing to obesity development may be expressed as minor unhealthy choices of foods or as more severe forms of eating disorders. For some individuals, the negative mood associated with CMDs can be alleviated with the consumption of "comfort foods" that tend to include calorie-rich snack food rather than vegetables and fruits.[174-176,198,199] In the long run, using comfort foods as a coping strategy to regulate negative mood associated with CMDs may lead to weight gain. In others, CMDs are associated with more severe forms of eating disorders, either over- and under-consumption.[86,151,174,175,200-202] Binge eating is defined as eating abnormally large amounts of food in a discrete period of time, accompanied by a sense of lack of control over eating during the binge eating episode.[201] Negative mood has been shown to precipitate episodes of binge eating,[175,198] and binge eaters tend to eat in response to negative mood.[136,203] Given the

comorbidity between CMDs and binge eating disorder,[204,205] individuals with a binge eating disorder also often have CMDs, which may increase their exposure to negative mood. The tendency to over-eat in response to psychosocial stress may lead to the development of obesity in binge eaters who frequently have to cope with symptoms of CMDs.

In addition to the health behaviors discussed above, CMDs often involve sleep disturbances and insufficient sleep. Short sleep duration has been shown to increase BMI,[206-209] perhaps mediated by disturbances in cortisol secretion,[210] although not all studies have observed this association in longitudinal analysis [211]. The temporal association between obesity and sleep disturbances may also flow in the opposite direction, obesity causing sleep problems,[212] in which case sleep problems might mediate the effects of obesity on the development of CMDs.

In addition to the unhealth behaviours described above, symptoms of CMDs may also lead to heightened functional limitations and bodily pain which, in turn, may increase the risk of weight gain due to decreasing physical activity (cf. the opposite direction of causality involving physical functioning and bodily pain in section 2.2.1). However, this mediational pathway appears unlikely because prospective studies have found little if any evidence for depression causing bodily pain or functional limitations related to physical constraints.[213,214] Thus, physical limitations and bodily pain are more likely to mediate the effects of obesity on CMDs (see section 2.2.1) rather than vice versa.

3.2.3. Low self-efficacy and social support

In addition to reflecting negative mood and emotional symptoms, CMDs are often include a cognitive component related to negative thoughts and attitudes toward the self. In particular, individuals suffering from depression and anxiety tend to have low *self-efficacy*, defined as a person's judgement about her or his abilities to achieve goals and to overcome challenges [215-217]. In the context of obesity and weight control, low self-efficacy reduces a

person's expectancies of successful weight management, leading to increased risk of developing obesity.[218,219] Obese individuals tend to have lower weight-related self-efficacy, and in participants of weight loss programs, individuals with low weight-related self-efficacy are less successful in losing weight during the program.[218] In fact, subjectively predicted weight loss in individuals who are trying to lose weight is a good predictor of actual weight loss,[220] which may explain why individuals with CMDs, and thereby low self-efficacy, have a greater risk of weight gain and obesity.

CMDs may not only undermine an individual's personal perceptions of self-efficacy, but in the long run also reduce the social support they receive from other people. CMDs have been shown to increase risk of strain and erosion of social support provided by friends, family members, and relatives.[221] Social support, in turn, is an important determinant of health,[162-166] and in the context of weight management, high social support from others has been associated with more successful attempts of weight loss.[222] Weight loss programs employing help from friends and significant others are more successful than programs based only on the input of the individuals attempting to lose weight.[223] Social support has also been demonstrated to sustain the maintenance of weight loss over time.[224,225] Persons suffering from CMDs, and who therefore have less social support from friends and family, may therefore be less able and motivated to control weight, which increases their risk of developing obesity.

3.2.4. Antidepressant use

Commonly used pharmacologic treatments for depression and anxiety disorders may have side-effects that result in weight gain, weight loss or both, depending on the individual and the length of treatment, among other factors.[226-230] Many psychotropic drugs with antipsychotic, mood stabilizing, and antidepressant properties are associated with weight gain. Among antidepressants, at least amitriptyline and mirtazapine, and the antipsychotic

drugs chlorpromazine, clozapine, and olanzapine may also cause weight gain. Minimal weight gain and decreases in appetite have been associated with the commonly used selective serotonin reuptake inhibitors.[231] Other psychotropic drugs, such as fluoxetine, isocarboxazid, nefazadone, topiramate, and psychostimulants, in turn, may cause weight loss. However, a review of the literature found that for most antidepressants the average effects on subsequent weight change are unclear, and that these may depend on the specific drug, the dosage, and the duration of treatment.[231] Thus, although antidepressant use is often suggested as a plausible mechanism accounting for the association between CMDs and obesity, the variability of the weight response to antidepressants and the low prevalence of antidepressant use among individuals with CMDs (between 3% and 6% depending on age group, see[232]) seem to suggest only a minor role for antidepressants in explaining the overall association between CMDs and obesity.

Chapter 4. Moderating factors in the association between obesity and common mental disorders

Given the potential mechanisms underlying the bidirectional association between obesity and CMDs, it is reasonable to hypothesize that the association is also moderated by certain factors. This is because the prevalence of the potential mediating mechanisms - and thereby the strength of the obesity-CMD association is likely to vary according to certain moderators. The present thesis examines six prominent moderator candidates: age, sex, socioeconomic status, chronicity of obesity, chronicity of CMDs and secular trends.

4.1. Age

Studies of obesity and age show that the prevalence of obesity increases with age, at least until late middle age.[233] In older ages, obesity rates may begin to decline, with little variation by gender or race.[234-236] For instance, in the National Health and Nutrition Examination Survey the prevalence of obesity was higher among persons 45 and 64 years of age than those under 45 or over 65.[233] Many people aged 75 and older may lose weight due to age-related loss of muscle mass or onset of disease and its treatment,[237] decreasing BMI in old age. However, most of the data on development of BMI in old age is based on cross-sectional data, in which age effects may be confounded by time period and birth cohort effects.

CMDs often have an early onset, indicating that their incidence is highest in adolescence and young adulthood, and slows down thereafter.[52] The prevalence of CMDs, by contrast,

increases between adolescence and middle age, and then decreases up to early old age.[68,238-243] The data on the course of CMDs in old age after age 75 is limited and the results have been mixed; while some studies report lower prevalence of CMDs in old age,[68] other studies have observed old age to be associated with increasing risk of depression and lower life satisfaction,[244-248] suggesting that mental health may deteriorate in the very old after the improvement observed around the age of retirement.

The association between obesity and CMDs might either strengthen or weaken with age. First, assuming that the influence of obesity on CMDs is mediated by bodily pain and limited physical functioning caused by chronic illnesses (see section 2.2.1), one would expect the obesity-CMDs association to strengthen with age, because these correlates of obesity become increasingly common at older ages.[25,249-252] In the meta-analysis of Luppino et al.,[103] there was a marginally significant moderating effect (p=0.07) for age when predicting depression risk in overweight/obesity vs. normal weight participants (OR=1.05, OR=1.48, and OR=1.77 for age groups <20y, 20-60y, and 60+, respectively) but this was not seen for obesity (ORs for the three age groups 1.70, 1.34, and 1.98; p for interaction p=0.52), providing only provisional evidence for a strengthening association.

On the other hand, the psychologically distressing effects of obesity may attenuate with age if the association between the two is driven by social stigma, discrimination, and negative self-image - assuming that the latter factors become less important for people's mental health as they become older. In a sample of 9991 overweight and obese American adults,[24] weight-related quality of life impaired with increasing age in domains of physical function, sexual life, and work, indicating the more severe physical strain caused by obesity at older ages. By contrast, increasing age was associated with fewer weight-related impairments in domains of self-esteem and public distress,[24] suggesting that the psychosocial impairments, perhaps due to social stigma and negative self-image, may diminish with age. In another study,[122] American men and women rated pictures of

individuals differing in age, sex, and body weight. The ratings included six dimensions: attractiveness, intelligence, happiness, job aptitude, success at relationships, and popularity. Obesity decreased ratings of attractiveness more strongly in young than in old people. Although such an interaction effect was not observed for other dimensions assessed in the study, the finding suggests that negative attitudes toward obese people may attenuate when people are judging older people.

Regarding the other direction of causality, the influence of CMDs on the development of obesity, the possible age interaction appears to be the opposite to the results of the meta-analysis[103] cited above. In particular, there appears to be a difference between adolescents and adults on the one hand, and between younger and older adults on the other hand. In the other meta-analysis assessing the effects of depression on obesity risk and weight change,[151] depression increased the risk of obesity more strongly in adolescents (OR=2.31, 2.06-2.58) than in adults (OR=1.25, 1.14-1.38). Of the 11 studies in adults, 5 provided evidence suggesting that depression increases the risk of obesity whereas 3 suggested that depression in associated with lower risk of obesity. Although there were too few studies to stratify the results according to the total age range, depression appeared to be associated with lower risk of obesity, or lower weight gain, especially in studies with older participants while positive associations between depression and later obesity were observed in younger adults. Thus, the influence of CMDs on obesity risk may attenuate or even become reversed with age. In the meta-analysis of Luppino et al., there was no significant age interaction when depression was used to predict the risk of obesity (ORs 1.76, 1.27, and 1.40 for age groups <20, 20-60, and 60+). For the association between depression and overweight, there was some suggestion of attenuation with age (OR=1.43, 0.83-2.47 for age <20; OR=0.96, 0.81-1.41 for age 20+) but this interaction was not statistically significant (p=0.22).

4.2. Sex

CMDs are almost twice as common in women as in men.[68] Sex differences in obesity in Britain are modest (23% in men, 25% in women;[45]). Obesity is often assumed to be more psychologically taxing for women than men, and there is some empirical evidence to support this assumption.[134,253,254] It has been argued that obese women are stigmatized and discriminated more than obese men, because appearance is more important for women than men, causing obese women to have poorer self-image and other psychological problems with their weight.[112-115] However, many of the prospective studies reviewed above have reported similar associations between obesity and CMDs in both sexes,[89,93] and some studies have reported stronger effects in men than in women.[91,92,99] Evidence regarding sex differences in the prospective effects of CMDs on the risk of obesity also suggests similar effects in men and women.[139,140]

In the meta-analysis by Blaine,[151] the associations of depression with future obesity or weight gain were very similar in men (4 studies, OR=1.34, 1.14-1.58) and in women (11 studies, OR=1.26, 1.20-1.32), and no significant sex differences in either directions of causality between obesity and depression were observed in the meta-analysis of Luppino et al.[103] Thus, in contrast to the commonly held assumption that obesity and depression are more strongly related in women than in men, the empirical evidence to date suggests no substantial differences between the sexes.

4.3. Socioeconomic status

Obesity and CMDs are both related to socioeconomic status (SES) with the socioeconomically disadvantaged having higher rates of obesity and CMDs than their socioeconomically more advantaged peers [68,255-261]. Given that obesity is less prevalent among those with high SES, people with high SES are more likely to compare themselves with

leaner peer groups, on average, than people with low SES. Due to the higher social salience of obesity in groups with lower prevalence of obesity, obese people with high SES may be more stigmatized and they may perceive themselves more negatively than obese people with low SES.[125,126,258] Indeed, there is some evidence to suggest that people with high SES hold more negative attitudes toward obesity than people with low SES.[126,258] A similar hypothesis has been put forward to explain why obesity is often more strongly correlated with CMDs in White than in Hispanic or Black populations, as obesity is more common among the latter groups.[262-265] If, on the other hand, CMDs cause obesity, it is possible that this effect is more easily observed among those with low obesity rates, such as people with high SES.[87] Based on the assumption that obesity is stigmatized differently in different subpopulations of the society, at least three studies have hypothesized that SES might modify the association between obesity and CMDs.

In the Midtown Manhattan Study of 1660 Americans aged 20 to 39 years,[266] obesity was associated with higher risk of depression in women with high SES but with lower risk of depression in women with low SES, suggesting that obesity was mentally distressing only for women with high SES. No effect modification by SES was observed in men. A similar interaction effect was observed in the cross-sectional U.S. National Comorbidity Survey Replication (NCS-R) study of 9125 participants who were administered the World Health Organization Composite International Diagnostic Interview assessing a range of mental disorders.[87] The association between obesity and mood disorders increased in strength with increasing educational level (ORs 1.10, 1.20, 1.42, and 1.44 from the lowest to the highest educational group). Unlike in the Midtown Manhattan Study, there were no sex differences in the interaction effect.

In the U.S. National Health and Nutrition Survey, men with depressive symptoms on average gained 3kg more weight than non-depressed men.[146] This association was stronger in men with less than 12 years of education than in men with higher education

(6.2kg vs. 1.2kg), suggesting a moderating effect for education opposite to that in the two studies above, and the presences of sex differences compared to the absence of sex differences in the Midtown Manhattan Study.

4.4. Chronicity of obesity and common mental disorders

Many of the psychiatric disorders tend to be chronic, and, after the initial onset, recurrent episodes later in life are highly likely.[52,154] Chronicity and recurrence has been studied particularly in relation to major depressive disorder,[267-272] as recurrent depressive episodes are known to progressively increase susceptibility to subsequent episodes. In one of the studies demonstrating this pattern,[271] the risk of a future episode of depression increased by 16% with each successive episode, and a commonly cited estimate suggests that 60% of individuals who become depressed for the first time will have another depressive episode, 70% of individuals who have had two depressive episodes will have a third, and 90% of individuals with a history of three depressive episodes will have a fourth episode.[154,155] The continuity of obesity has not been studied with the same methodological framework as recurrent depression, but longitudinal studies of BMI and obesity have demonstrated substantial stability of obesity over age.[273]

The severity of CMDs and obesity have been suggested to be moderating factors in the association between obesity and CMDs,[274,275] so that associations might be strongest among those with severe psychological distress and morbid obesity, although empirical tests for this hypothesis remain scarce. Severity of obesity and CMDs is often conceptualized as extreme values of BMI and CMDs measured at one point in time. However, it may be more useful to consider severity in terms of temporal stability. Long-term obesity and chronic/ recurrent CMDs are likely to have different health consequences than those related to more temporary weight gain or psychological distress.

Two previous studies support the moderating role of chronicity in the association between obesity and CMDs for both directions of causality. In the study of New Zealand adolescents described earlier in section 3.1.,[139] depression in early and late adolescence increased the risk of adult obesity in women. The prevalence of adult obesity increased linearly with the number of assessment periods at which the women were depressed. Among women who had not been depressed in any of the assessment periods, 10% were obese. The proportion of obese women increased to 16% among those who had been depressed in one assessment period, and to 21% among those who had been depressed in two or more assessment periods. In the Great Smoky Mountains Study[99] obesity was assessed in childhood and adolescence, and the results showed that only chronic obesity (obesity at all the 4 measurement times across childhood and adolescence) was associated with increased depression risk 8 years later, while obesity in childhood or adolescence measured in one point in time was not related to depression risk.

Similar results have been obtained in two smaller studies of bipolar disorder and weight gain. In a small (n=50) sample of individuals with bipolar disorder,[276] overweight and obese individuals had more previous recurring episodes of depression than normal-weight individuals. In a larger sample (n=175) of individuals with bipolar diagnosis,[276] obese participants had more previous depressive and manic episodes, higher baseline depressive symptoms, and required more time in acute treatment to achieve remission from depressive episodes. Obese participants were also more likely than non-obese participants to experience a recurrent depressive episode during the period of treatment maintenance, the time to recurrence also being shorter for obese than non-obese individuals. These two studies with small and non-representative samples thus suggest that obesity may be related to more recurrent episodes of depression. However, it is unclear how these results generalize to non-patient samples because the reported patterns of weight gain may have been caused by medication or other disorder-specific associations related to bipolar disorder.

4.5. Secular trends

As reviewed above, the increasing prevalence of overweight and obesity is well established,[6,37,45,46,277-279] and the age-specific obesity rates appear to have increased with successively younger birth cohorts.[280,281] Analyses of secular trends in CMDs have produced less consistent results.[282] Early studies examining the time periods between 1970s and 1990s suggested increasing rates of depression in the United States,[283] Sweden,[284] and Britain[285] but not in Finland[286] and Canada.[287] But these time-period effects, if accurate, do not seem to have continued after the 1990s. The incidence of diagnosed depression in the UK declined between 1993 and 2005.[288] According to the British Psychiatric Morbidity Survey,[68,289,290] the rate of CMDs has remained constant between 1993 and 2007, although the prevalence of 'mixed anxiety and depressive disorder' increased by 14% between 1993 and 2000.

Secular trends in the association between obesity and CMDs might be hypothesized especially if the association was driven by social stigma and discrimination. With an increasing number of people being obese today compared to 20 years ago,[45] one could expect that the adverse mental health effects of obesity would attenuate with time as overweight and obesity have become more common and thereby normalised in the society. On the other hand, the obesity epidemic is increasingly considered as a serious health threat not only to obese individuals but to the society as a whole with increasing health costs accruing from treating medical conditions caused by obesity.[291] This might increase the stigma of obesity and negative attitudes toward obese people despite the increasing prevalence of overweight and obesity in the population.[292] Prevailing negative attitudes toward obesity might also be expected based on studies showing that even obese people tend to hold anti-obese attitudes, [120,122] indicating that person's own weight does not necessarily change attitudes toward obesity more positive. However, no studies have assessed whether the association between obesity and CMDs has changed over time.

Chapter 5. Study aims and hypotheses

Most previous longitudinal studies of obesity and CMDs have investigated the temporal association using a standard longitudinal settings in which the outcome is measured some years after the exposure, with some studies including adjustment for the outcome value at baseline or excluding baseline cases. While these studies have suggested a bidirectional association between obesity and CMDs,[103] the association may be more nuanced or complex than this standard longitudinal model would lead one to assume. The purpose of the present thesis is to take advantage of repeated measurements of BMI and CMDs over an extended follow-up period, and to examine the bidirectional association between obesity and CMDs using various alternative longitudinal statistical methods. These include the assessment of age-related trajectories to examine how the associations may change with age; lagged longitudinal models with alternative follow-up intervals to examine whether the associations change as a function of length of follow-up; change vs. change analysis to examine whether within-individual changes in obesity are associated with changes in CMDs, and vice versa; and cumulative exposure scores to examine whether measurement of obesity or CMDs as the exposure variable over a long period of time provides additional information on the temporal dynamics of the associations. In addition, based on the literature of potential mechanisms (reviewed in sections 2.2. and 3.2.) and modifying factors (reviewed in Chapter 4), the role of several sociodemographic and health-behaviour covariates in mediating or moderating the associations between obesity and CMDs is assessed.

The analysis is based on observational data. Such data without experimental randomized manipulation controlled by the researcher are subject to omitted variable bias, i.e., it is not possible to exclude alternative explanations for the observed association

between the variables of interest, because these association may be caused or confounded by third variables not included in the model, and it is never possible to be sure that all relevant variables have been included. Definite causal inferences cannot therefore be derived from observational data alone. Experimental study designs in which the researchers are able to manipulate the exposure of interest, such as randomized controlled trials (RCTs), are the gold standard to establish causal effects.

Experimental study designs are not impossible in the context of obesity and psychological distress. Studies in clinical samples, such as morbidly obese patients undergoing bariatric surgery, show that the major weight loss is often accompanied by improving mental health after the procedure.[293-300] There is also evidence to suggest that various treatments of depression may affect weight, either increasing or decreasing it.[230,276,301-304] However, it is unclear how accurately the results from these studies can be generalized to the general population or to more average levels of BMI or depression, e.g., whether more moderate weight changes than those associated with bariatric surgery lead to changes in mental health in individuals without morbid obesity requiring surgical treatment. It may also be added that most experimental studies cited above do not qualify as randomized controlled trials because individuals usually seek treatment themselves rather than being randomly allocated to different treatment groups.

The interpretation of findings from studies of depression treatment and weight change is also complicated by other reasons. Many of these studies are based on pharmacological treatments in which weight changes may be caused by side effects of medication rather than the alleviation of mental health problems.[231] Other depression treatments may explicitly include physical activity or dietary changes as part of the treatment,[302,305] in which case it is not possible to separate their direct effects from the effects of mental health improvement on subsequent weight change. Furthermore, short-term randomized controlled

trials are not necessarily informative regarding long-term effects of obesity and psychological distress cumulating over several years or even decades.

Given the limitations of randomized controlled trials in this context, one of the best available methodological approaches to examine the association between obesity and CMDs is a prospective longitudinal study in which both obesity and CMDs are assessed repeatedly over time. Although observational data cannot definitely establish causal relations, and correlations do not imply causation, the absence of certain associations and the presence of others should help one to make sound inferences about the potential mechanisms connecting obesity and CMDs with each other over time.

Accordingly, bidirectional associations between obesity and CMDs were addressed with the following steps: First, changes in obesity and CMDs with age and time were characterized. Second, temporal associations between obesity and CMDs were examined with alternative lagged longitudinal models, including measurement of the exposure with a cumulative score taking into account exposure status with repeated measures over several years. Third, exposure and outcome measures were determined using within-individual change scores, which provide a more reliable method of investigating potential causal associations without confounding by between-individual differences in unmeasured covariates. This analysis also examined whether increases vs. decreases in the exposure over time were qualitatively differently associated with the outcome in the future. Fourth, a number of covariates were included in the analysis to test whether these covariates explained any of the association between obesity and CMDs. Fifth and finally, interaction effects with age, sex, socioeconomic status, chronicity and time-period were assessed to test whether the associations between obesity and CMDs varied according to these covariates. The following introduces these study objectives and related hypotheses in a greater detail.

5.1. To characterize age-related and cumulative patterns of obesity and common mental disorders

Age trajectories: As reviewed above, the age-related development of obesity and CMDs both appear to follow a non-linear trajectory. Accordingly, their prevalence increases from adolescence to midlife but begins to decrease, or at least reaches a plateau, in late middle age or old age,[233,234,238-242] although some studies in older populations have reported an increasing risk of CMDs after age 75.[244-248]

> *Hypothesis:* It was hypothesized that the rates of obesity and CMDs in the present sample of adults between 35 and 79 year would increase up to middle age but that this increase would then slow down and eventually decrease. In addition to assessing how obesity and CMDs are related to age, the role of birth-cohort effects in modifying the age trajectories was also investigated. Furthermore, the age trajectories of within-individual change scores in BMI and CMDs were examined to test whether the effects of age observed at the group level (between individuals of different ages) were also replicated at the individual level, giving more robust evidence of the true aging effects.

Cumulative development: Previous studies of socioeconomic disadvantage,[260,306,307] smoking,[308] childhood risk factors[309-311] and other life-course exposures[312-314] have modeled these variables taking into account the accumulation of the exposure over time.[315,316] A life-course perspective suggests that assessing the exposure only in one point in time may be insufficient to capture the true effects of the exposure, which evolve over longer periods of time. While several studies have reported substantial inter-individual stability in BMI and

CMDs,[139,273,312,313,317] these longitudinal studies have rarely examined how the long-term history of obesity or CMDs condition the future course of these characteristics. Research on clinical depression has demonstrated that the risk of depressive episodes increases progressively with the number of recurrent episodes, suggesting that chronic depression makes people more sensitive to environmental stress and thereby increases the risk of future depression.[154,156] Whether a similar cumulative pattern is observed for obesity and self-reported CMDs is unknown.

Hypothesis: Based on findings on the recurrence of depressive episodes, a similar accumulating pattern of recurrence is hypothesized to apply to self-reported CMDs as well, that is, the risk of future CMDs increases progressively as a function of the proportion of times the person has reported symptoms of CMDs at previous examinations. Although no similar theoretical background exists for obesity, it is plausible that the development of obesity is also characterized by a progressively increasing risk, i.e., the more times a person has been obese at previous study phases, the higher the risk of obesity in the future.

5.2. To assess the temporal associations between obesity and common mental disorders

Lagged longitudinal analysis: With some exceptions,[88,89] most of the earlier studies of obesity and CMDs have examined the issue of temporality in the same study only in one direction, i.e., whether obesity predicts later CMDs or vice versa. Meta-analysis of all available studies in both directions suggests a bidirectional association between obesity and depression with almost equal effect magnitudes (about 50% increased risk) for both

directions.[103] However, differences between studies, including sample compositions, measures and other study design characteristics, may introduce variability and bias in the total estimates pooled over different studies. It is therefore important to examine the bidirectional association between obesity and CMDs in the same sample and with the same measures.

Hypothesis: Previous studies have provided evidence in favour of both temporal directions for the association between obesity and depression. It was therefore hypothesized that there is a bidirectional longitudinal association between obesity and CMDs. To test the role of length of follow-up period in these associations, separate models were fitted with the outcome assessed 5, 10, 15, and 20 years after the assessment of the exposure. To test the robustness of the temporal associations, the longitudinal models were also fitted with adjustment for outcome measurement at baseline, which is the standard longitudinal method to examine temporal associations between exposure and outcome.

5.3. To examine associations between within-individual changes in BMI and common mental disorders

Concurrent changes: If the associations between obesity and CMDs are causal, one would expect that changes in one follow changes in the other. Analysis of interrelated within-individual changes in two variables provides a more reliable method of establishing potential causal effects than analysis of between-individual associations, which may be confounded by unobserved variables that vary between individuals. Within-individual analysis excludes the possibility of stable unobserved characteristics confounding the

associations, although it still leaves open the possibility that changes in some unobserved variables account for the observed associations between the exposure and outcome of interest. Given that categorical measures of obesity and CMDs would provide only crude measures of changes over time, the change analyses were carried out with continuous measures of BMI and symptoms of CMDs. The first set of within-individual analysis assessed whether changes in BMI and CMDs over two consecutive study phases were correlated with each other, i.e., whether change in BMI is accompanied by concurrent change in CMDs, and vice versa. This is the common method of change versus change analysis.

> *Hypothesis:* Previous studies have suggested that high BMI increases the risk of CMDs and that CMDs increase the risk of obesity. If these associations reflect causal effects, one would hypothesize concurrent changes in BMI and CMDs scores to be related to each other.

Time-lagged changes: Correlations from concurrently assessed within-individual changes in two variables cannot be used to determine the temporal order of the changes. This obviously limits the possibility of making causal inferences, as temporal precedence is an essential requirement for demonstrating a causal effect. To separate the temporal order of changes in BMI and changes in CMDs over time, the concurrent change analysis was complemented with a time-lagged change analysis in which change in the exposure variable between two study phases was used to predict later change in the outcome between two subsequent study phases, e.g., change in BMI between examinations 1 and 2 predicting change in CMDs between exminations 2 and 3. This setting enables the evaluation of long-term changes in the outcome that are preceded by earlier changes in the exposure and, as long as the associations between BMI and CMDs hold over such long time periods, it should provide stronger evidence for a causal association than the analysis of concurrent changes.

Hypothesis: Evidence from several longitudinal studies suggest that obesity and CMDs are related to each other even over long periods of time, e.g., when adult risk of depression is predicted by adolescent obesity. It was therefore hypothesized that the lagged change analysis would replicate the findings from the concurrent change analysis described above.

Non-linear change: The time-lagged analysis of change can be used to assess the issue of reversibility of the association between BMI and CMDs. Reversibility refers to situations in which the removal of the causal exposure of interest leads to a reduced risk of the outcome, since one of the causal factors contributing to the risk has been removed. Reversibility is often considered as evidence for a causal association between two variables of interest.[318-320] For instance, obesity is known to be associated with risk of asthma, and weight loss has been shown to alleviate symptoms of asthma, demonstrating reversibility and providing additional evidence for a causal effect of obesity on the development of asthma.[321] However, a causal effect can also be irreversible; thus, lack of reversibility is not a strong argument to refute a causal hypothesis.

To address the issue of reversibility between BMI and CMDs in the present study, the time-lagged change analysis was modified to assess whether there was a qualitative difference between either a decrease or an increase in the exposure and future change in the outcome. A reversible causal association should be observed for both directions of change, i.e., weight gain leading to increase in CMDs and weight loss leading to decrease in CMDs, and vice versa. On the other hand, the causal association may flow in one direction only. Perhaps weight gain increases symptoms of CMDs but weight loss is unrelated to future changes in symptoms of CMDs. This pattern would imply a ratchet-like effect in which weight gain would be causing CMDs but weight loss would not alleviate such symptoms, indicating absence of reversibility.

Hypothesis: There are no studies examining direction-specific associations between changes in BMI and CMDs, so there was no previous research to draw on in formulating hypotheses. However, assuming that the bidirectional associations reported in previous studies represent causal effects, one could hypothesize that there is no qualitative difference between increasing and decreasing exposure, i.e., a decrease in BMI predicts a decrease in CMDs and an increase in BMI predicts an increase in CMDs, and vice versa.

5.4. To assess whether the associations between obesity and common mental disorders are confounded or mediated by certain sociodemographic or health-behaviour covariates

As reviewed in sections 2.2 and 3.2., multiple mechanisms have been proposed to account for the potential influence of obesity on CMDs and the influence of CMDs on obesity risk. The Whitehall II dataset, the study used in this thesis, includes several measures with which to test for some, but not all, of these potential mechanisms. The covariates assessed in the present study included socioeconomic status, physical pain, dietary patterns, longstanding illnesses, physical activity, smoking, and alcohol consumption. These variables may represent confounders affecting both obesity risk and CMDs, or mediators through which the effects of one are propagated on to the other.

Hypothesis: While several mechanisms have been suggested to explain the bidirectional association between obesity and CMDs, empirical tests of these mechanisms remain scarce. It was hypothesized that socioeconomic status, physical pain, dietary patterns, longstanding illnesses, physical activity,

smoking, and alcohol consumption may account part of the bidirectional obesity-distress association.

5.5. To examine whether associations between obesity and common mental disorders are modified by sex, age, socioeconomic status, and time-period effects

The fifth objective seeks to identify factors that modify the associations between BMI and CMDs, assessed using the different statistical models introduced above. As reviewed earlier, a number of studies have investigated sex, age, socioeconomic status and chronicity in particular, as potential effect modifiers. Although some evidence has been gathered to support their role as moderators, the findings have been inconsistent and at least yet insufficiently reliable to make any firm conclusions. In addition to these three factors, the present study explores the role of time-period effects discussed in the previous section.

Sex: Despite the common belief that obesity and CMDs are more strongly related in women than in men, previous longitudinal studies have reported inconsistent or no sex differences.[103,151]

Hypothesis: Given the mixed findings from previous studies, we expected to observe no consistent sex differences in the associations between obesity and CMDs.

Age: With respect to age, two competing scenarios can be considered. On the one hand, chronic pain and disabling physical conditions become more prevalent at older ages. Insofar as the association of obesity with CMDs reflects the adverse effects of bodily pain and limits to physical functioning, the obesity-CMDs relationship could be expected to strengthen with

age. On the other hand, the adverse effects of obesity may reflect social stigma and discrimination. If these social factors are the driving forces behind the influence of obesity on CMDs, then the association could be expected to weaken with age, because older people seem to be less stigmatized and discriminated against because of their obesity than younger people (see previous section for discussion). There appears to be no a priori reason to hypothesize that the influence of CMDs on obesity risk would change with age.

> *Hypothesis:* There are limited data addressing age interactions in the association between obesity and CMDs, so strengthening and weakening associations with age are equally plausible.

Socioeconomic status: As reviewed earlier, some studies have suggested that the influence of obesity on CMDs is stronger in individuals with high socioeconomic status,[87,266] perhaps due to stronger social stigma associated with obesity among social groups in which obesity is not as common. No similar hypotheses of moderating effects of SES have been presented in relation to the other direction of causality, i.e., for the influence of CMDs on obesity risk.

> *Hypothesis:* Higher SES strengthens the association between obesity and CMDs.

Chronicity: The development of CMDs in response to obesity, and vice versa, may require a long time period with accumulated exposures over time only resulting in observable effects in the population. Assuming that the associations of obesity and CMDs exhibit a similar accumulating effect pattern as some of the variables mentioned in Aim 1 (e.g., smoking, socioeconomic disadvantage), one would expect the association between obesity and CMDs to strengthen when measures of persistent obesity and persistent CMDs are used as the exposure variables.

Hypothesis: Participants who are obese at several repeated measurements are more likely to have CMDs than individuals who are obese only at one or none of the repeated measurements. Similarly, recurrent CMDs over the observation period are more likely than CMDs that occur at a single measurement phase in increasing the risk of future obesity. To test these hypotheses, cumulative scores of obesity and CMDs were created as sum scores calculated over several follow-up phases.

Secular trends: If the overall prevalence of obesity in the society is relevant for the effects of obesity on CMDs of obese individuals, one would expect that the association of obesity with CMDs might have attenuated over time from 1980s to 2000s, as the increasing prevalence of obesity may have mitigated the social stigma attached to obesity. On the other hand, the negative health consequences of obesity have received increasing attention in the media and in public health discussions, which may have made obesity a more salient risk factor for CMDs. There appears to be no reason to expect that the effects of CMDs would have become more or less important over time in affecting obesity risk.

Hypothesis: The association between obesity and CMDs may weaken or strengthen with time, depending on the societal dynamics underlying the potential time-period effects.

Chapter 6. Methods and materials

6.1. Background

The original Whitehall study (Whitehall I) was set up in 1967 and was based on a sample of 18403 middle-aged men, all employed in stable jobs in the British Civil Service. One of the main findings of this study was an inverse social gradient in mortality: the lower the grade of employment, the higher the risk of death. Ten-year follow-up showed that there was a steep inverse relation between grade of employment and death from all causes, from coronary heart disease, and from noncoronary causes.

The first Whitehall study made clear that inequalities in health were not limited to the health consequences of poverty. This raised the question of why there should be a social gradient in disease in people above the poverty threshold. Even when conventional risk factors were taken into account, two-thirds of the mortality risk differential between the clerical and administrative grades remained unexplained. The Whitehall II study, a new longitudinal study of British civil servants, was set up in 1985 with the explicit intention of examining reasons for the social gradient in health and disease in men and extending the research to include women.[322,323] The main hypothesis of the study was that psychosocial factors and aspects of diet and nutrition might fill the unexplained part of the social gradient in mortality.

6.2. Study population

Whitehall II is a British occupational cohort study. The target population for the study was all civil servants (men and women) aged 35–55 years working in the London offices of

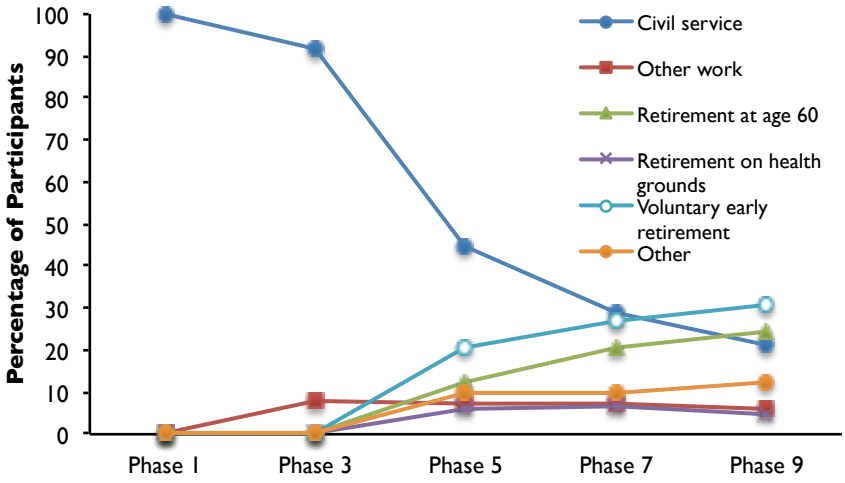


Figure 1. Proportion of participants by employment status and study phase.

20 Whitehall departments in 1985–88. The achieved sample size was 10 308 people: 3413 women and 6895 men. The participants were from clerical and office support grades, middle-ranking executive grades, and senior administrative grades. Most participants have remained in the civil service while others have moved elsewhere to work, but increasingly the sample consists of individuals who have retired, as shown in Figure 1.

6.3. Study design

The whole cohort is invited to the research clinic at 5-year intervals (study phases 1, 3, 5, 7, and 9), and a postal questionnaire is sent to participants between clinic phases (study phases 2, 4, 6, and 8). The 9 data collection phases were carried out in 1985-1988 (n=10308), 1989-1990 (n=8133), 1991-1993 (n=8637), 1997-1999 (n=8629), 2001 (n=7344), 2002-2004 (n=6967), 2006 (n=7173), and 2008-2009 (n=6761).[322] Home visits by nurses were offered for the first time in Phase 7 to participants unwilling or unable to travel to the clinic. A brief telephone questionnaire is administered to those who decline clinic and full questionnaire

participation at each phase. The present study used data from the clinic phases of 1, 3, 5, 7, and 9 when height and weight were measured to assess BMI, and when the participants were administered questionnaires including measures of CMDs.

6.4. Procedures

Non-responders to all phases were followed up by two reminder letters and telephone contact where possible, either at work or at home. After phase 2 an increasing number of participants had to be mailed at their home address as they had either changed job, retired, or left the Civil Service for other reasons. Further attempts to trace non-responders were made through the Civil Service Pensions scheme and the OPCS's Family Health Service Authorities tracing service. Data quality was backed up verifying questionnaire, clinical screening data, and laboratory test results by double entry. All variables were subjected to range and validity checks and in cases of ambiguities that could not be solved, values were set to missing.

6.5. Study variables

6.5.1. Body Mass Index

BMI was calculated as weight (kilograms)/ height (metres) squared. Following the World Health Organization definition, participants with BMI 25 to 29.9 kg/m² were considered overweight and those with BMI>30 kg/m² obese.[1] Weight was measured in underwear to the nearest 0.1 kg on Soehnle electronic scales. Height was measured in bare feet to the nearest 1 mm using a stadiometer with the participant standing erect with head in the Frankfort plane. Repeatability of the weight and height measurements over 1 month (ie between-subject variability/total (between + within subject) variability), undertaken on 306 participants, was 0.99 at the Phase 7 screening.

6.5.2. Common mental disorders - General Health Questionnaire

CMDs were assessed using the 30-item self-administered General Health Questionnaire (GHQ) designed to be a screening instrument for use in community settings.[58-60,75,324,325] The original GHQ questionnaire consisted of 60 items asking about symptoms of depression, anxiety, and psychosomatic symptoms, but the shorter 30-item and 12-item GHQ questionnaires have become more popular and have been used in most recent studies using the GHQ.

The GHQ was developed as a self-administered questionnaire to detect undifferentiated CMDs in community samples and to act as a screening instrument for minor psychiatric disorders. It is not a specific measure of depressive or anxiety symptoms but rather extracts information on general psychological distress. The 30 items tap into symptoms of depressive, anxiety, neurotic, and stress-related disorders experienced "over the past few weeks." Sample items include statements such as "Have you recently been feeling unhappy and depressed", "Have you recently been able to concentrate on whatever you're doing" (reverse scored), and "Have you recently felt you couldn't overcome your difficulties". Each item has four response categories (1=not at all, 2=no more than usual, 3=rather more than usual, 4=much more than usual). This response format is intended to differentiate the GHQ from personality measures assessing relatively stable individual differences in psychosomatic symptoms.

The predictive validity of the GHQ is demonstrated by extensive previous research showing, for instance, that GHQ score is strongly associated with diagnoses of depressive and anxiety disorders,[59,60,326,327] mortality[77,328,329] and other health outcomes.[74,75]

The present study used the 30-item GHQ and two different methods of coding the GHQ scores were applied:

Dichotomous GHQ indicator: Given that the GHQ has been developed as a screening tool to identify potential "cases" of psychiatric illness, depressive and anxiety disorders in

particular, it is commonly coded as a dichotomous rather than a continuous variable.[58] Here the items are scored to indicate whether the symptom was present or not (0=not at all/no more than usual, 1=rather more than usual/much more than usual) and these 30 dichotomous scores are summed together. The sum score is then dichotomized using a cut-off value to differentiate "GHQ cases" from "non-cases". The optimal cut-off threshold in the Whitehall II cohort was identified as 0-4 vs. 5-30 on the basis of receiver operating characteristics analysis using data from clinical interviews.[325] At this threshold the sensitivity of the GHQ was 73% and specificity 78% against the Clinical Interview Schedule. Under this scoring system, at each phase the participants were defined either as GHQ cases (GHQ score ≥5) or "non cases" (GHQ score ≤4). The threshold for GHQ caseness has been used in several previous studies in this cohort[74,330,331] as well as in many other samples.[77,332]

Continuous GHQ score: In addition to the dichotomous GHQ indicator, a continuously coded GHQ score was used for the purpose of calculating GHQ change scores. A continuously coded scale retains all the available information on the person's GHQ level, and is therefore preferable than the dichotomous GHQ indicator to measure change over time. For this purpose, each GHQ item was coded with the 4-point scale (1=not at all, 4=much more than usual), and the 30 item scores were summed together resulting in a scale with theoretical range of 30 to 120.

6.5.3. Covariates

Occupational grade was measured by the participant's civil service employment grade assessed on a 6-point scale at baseline. Grade of employment was determined by asking all participants for their civil service grade title. Based on salary, the civil service identified 12 non-industrial grades that, in order of increasing salary, comprise clerical assistant, clerical officer, executive officer, higher executive officer, senior executive officer, and seven "unified grades". Other professional and technical staff were assigned to these grades on the basis of salary. As in previous reports from the Whitehall II cohort, unified

grades 1–6 were combined into one group and the bottom two clerical grades into another, producing six categories; here we coded the variable so that category 6 represents the highest status jobs and category 1 the lowest. In order of increasing occupational grades, the annual salary of the six groups in 1992 was between £7400 and £12000; £8500 and £17000; £14000 and £21000; £18000 and £25000; £25000 and £36000; and £29000 and £88000, respectively.[322] For retired participants and participants no longer working in the civil service, assigned SES was the final grade before leaving the civil service.

Alcohol consumption was coded from the participants's self-reports of the number units of alcohol the participant had consumed during the last week. The number of units of alcohol per week was then divided into three categories based on UK public health recommendations: 0=No alcohol consumption; 1=Moderate alcohol consumption (1-21 alcohol units per week for men, 1-14 portions for women); 2=Heavy alcohol consumption (more than 21 alcohol units for men, more than 14 units for women).

Physical activity was calculated using the participants' reports of their weekly hours of moderate and vigorous physical activity. Hours spent undertaking moderate and vigorous physical activity were summed together and divided into quartiles separately at each study phase.

Longstanding illness was self-reported by the participants by responding to a question asking whether the participant had any longstanding illnesses limiting daily activities (0=no, 1=yes).[333]

Smoking status was coded into three categories based on the participants' self-reported smoking habits (0=Never-smoker, 1=Ex-smoker, 2=Current smoker).

Sleep duration was measured by asking the participants about their normal sleep duration ("How many hours of sleep do you have on an average week night?"), which they reported on a 5-point scale (5 hours or less, 6, 7, 8, and 9 hours or more). At phase 3, the

wording of the question was slightly different: the participants were asked 'On an average weekday how many hours do you spend on the following activities; (a) Work, (b) Time with family, (c) Sleep?' Response categories were 1 – 12 hours. The responses to sleep question were collapsed to form categories identical to those at other phases.

Bodily pain interfering the participant's daily life was measured by the bodily pain subscale of the self-reported Short Form 36 (SF-36) health questionnaire.[334,335] The scale consists of two items, "How much bodily pain have you had during the past 4 weeks?" with response categories of None, Very mild, Mild, Moderate, Severe, Very Severe, and "During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?" with response categories of Not at all, A little bit, Moderately, Quite a bit, Extremely. The SF-36 questionnaire was introduced in the data collection at phase 3, so analyses including the SF-36 were carried out without data from phase 1.

Dietary patterns were determined using the self-reported 127-item Food Frequency Questionnaire (FFQ;[336-339]) in which the participants were asked about their normal dietary intake of various edibles. Alternative Healthy Eating Index (AHEI) score[340] was created by summing its nine component scores (fruits, vegetables, ratio of white to red meat, trans fat, ratio of polyunsaturated to saturated fat, total fibre, nuts and soy, alcohol consumption, and long-term multivitamin use); a higher score corresponded to greater adherence of a healthy diet. Data for dietary patterns were available at phases 3, 5 and 7.

6.6. Statistical methods - Multilevel regression

The data consisted of repeated measurements over 5 data collection points from the same individuals, so it was necessary to apply statistical methods capable of taking advantage of the repeated measurement data. In multilevel regression, also known as hierarchical or random-effect regression, observations are nested within higher-order

groups, such as pupils nested within classrooms or employees nested within companies.[341-344] Multilevel modeling can be applied in longitudinal analysis by structuring the data so that the repeated measurements (level 1) are nested within individuals (level 2). Thus, each participant can contribute multiple person-observations in the dataset, which allows one to pool repeated measurements in longitudinal studies into a single model. All individuals with data on at least one measurement time can be included in the model, so full data from all measurement times is not needed. The estimation method of multilevel models takes into account the non-independence of multiple observations nested within the same individuals.

The size of the sample that corresponds to the independent observations from repeated measurements in the same individuals, i.e. the effective sample size, depends on the degree of clustering of the outcome measure within individuals, also known as the intraclass correlation. If the outcome does not cluster within individuals, e.g., if measuring CMDs at one point in time would not predict a person's likelihood of reporting CMDs at another point in time, the intraclass correlation would be zero and the repeated measurements would effectively represent independent observations even if they had been collected from the same individuals. If, on the other hand, the outcome measured at one point in time strongly predicted the outcome at another point in time, the intraclass correlation of the outcome would be high and the effective sample size much lower than the number of person-observations from the same participants. For instance, collecting 10 repeated measurements of height over a 10-year period in a sample of 100 adults and treating the repeated measurements as 1000 person-observations nested within 100 individuals would not result in an effective sample size of n=1000, since adult height is so strongly clustered within individuals; repeated measurements of adult height would not substantially add statistical power in terms of sample size.

The estimation of coefficients in multilevel longitudinal regression combines two sources of variance: differences in average levels of the outcome between different individu-

als and individual-specific variation of repeated measurements around the individual's own average level of the outcome. In a longitudinal analysis with concurrently measured exposure and outcome variables at several measurement times, between-individual differences therefore represent cross-sectional associations comparing different individuals to each other while within-individual differences represent longitudinal associations comparing different measurement times within the same individuals. If the outcome of interest is highly stable over time within individuals (high intra-class correlation), between-individual variance gets more weight in the regression because within-individual variance accounts for a small portion of the overall variance - and vice versa.

Irrespective the relative strengths of between-individual and within-individual components of variance, it is possible to fit multilevel regression models taking into account only between-individual or within-individual differences. The latter is also known as fixed-effect estimation in the econometrics literature. However, this usage of this term will not be used here since fixed effect (vs. random effect) also has another meaning in the context of multilevel regression, as described below. In the present study, all multilevel models were fitted taking into account both between-individual and within-individual variance. Instead of fitting within-individual regressions, within-individual variance was modeled with change scores because this provided a more flexible and easy to interpret method to examine time-lagged associations and directions of change (increase vs. decrease in the exposure). The change score analysis is described in more detail in section 7.8.

Standard linear regression without repeated measurements is able to estimate only the fixed effects of covariates, whereas in multilevel regression, it is possible to introduce random effects, in addition to fixed effects, by taking advantage of the hierarchical structure of the data. For instance, in a study of pupils from several different schools, it is possible to examine how pupils' cognitive ability predicts their grades (fixed effect) and how this association between cognitive ability and grades varies over different schools (random effects)

and how these differences are related to school characteristics. In longitudinal models, it is possible to introduce random effects to examine individual-specific trajectories over time. Such random effects were not a topic of interest in the present study, so all the regression models were fitted with random-intercept models only, i.e., the regression models estimated separate intercepts for each participant based on their repeated measurements of the outcome, but no random effects for any of the covariates included in the models were introduced. The random parts of the models are therefore not shown in the results.

Chapter 7. Results

The presentation of the results is structured as follows: Section 7.1. presents the descriptive statistics of the sample and the subsamples used in different models. Section 7.2. examines the attrition patterns over the study period and creates an indicator of attrition pattern to be included as a covariate in subsequent analyses. Sections 7.3. and 7.4. investigate how BMI and CMDs develop over age and time. Sections 7.5. and 7.6. present the standard regression analyses in which the exposure is measured at baseline in study phase 1 and the outcome is assessed cross-sectionally or longitudinally after 5 to 20 years in separate regression models. Section 7.7. repeats these analyses using multilevel regression to pool the data over all study phases. Section 7.8. moves to examine how changes in the exposure are related to changes in the outcome both concurrently (over the same time period) and longitudinally in time-lagged models. In section 7.9., the exposure is modeled as a cumulative score taking into account exposure status over several study phases. Section 7.10. evaluates the role of several potential mediating or confounding factors in the models fitted in previous sections, and section 7.11. examines potential moderator variables in these associations.

As noted in the Declaration of Authorship on page 2, part of the results have been previously published in academic journals (ref. [345] for the cumulative development of CMDs; ref. [346] comparing cumulative and non-cumulative exposures; ref. [347] for the age interaction between obesity and CMDs). However, none of the present results exactly replicate the earlier results because (1) the present analysis includes new data collected at phase 9 not included in the previous studies and (2) the present analysis takes a somewhat different approach than the previously published analyses. Thus, all the previously published material have been incorporated to the broader multilevel methodology framework developed for the present thesis. First, the previous analysis of age-related trajectories of obesity and CMDs[347] examined only the relationship between cross-sectionally assessed obesity and CMDs. Thus,

the age interaction was not examined in relation to time-lagged longitudinal models examining different temporal orders between obesity and CMDs or to other longitudinal models explored in the present thesis, such as the change versus change analysis. Second, the previous analysis of cumulative patterns[346] used the repeated measurements only to create the exposure variable whereas the outcome variable was only measured at one time point at the end of the follow-up. The present analysis applies a more comprehensive multilevel approach by using repeated measurements for the outcome as well (as was done in ref. [345]). Third, the cumulative patterns of CMDs explored in ref. [345] are only of secondary interest in the present context, because that paper was mainly interested in the chronic development of CMDs and not in the relationship between obesity and CMDs.

All analyses were fitted with STATA 11.1 statistical software. The program code for all the analyses presented in the results section are reprinted in the Appendix.

7.1. Descriptive statistics and sample composition

Purpose: The section presents basic descriptive statistics for the sample, and compares the subsamples included in subsequent cross-sectional and longitudinal multilevel regression models. A flowchart describing the sample composition by study phase is also provided.

Methods: Descriptive statistics (means and standard deviations for continuous variables, percentages and numbers of participants for categorical variables) are calculated separately for each study phase and for different subsamples. The number of participants with relevant data available is illustrated with a flowchart.

To have a more detailed picture of distributions of BMI and GHQ beyond means and standard deviations, density distributions of the two variables are plotted separately for each study phase. This is accomplished with kernel density estimation, which plots the distribution of the variable with a moving window over which the values are averaged. In contrast to the commonly used histogram, which represents a kernel estimation method in which the data are divided into discrete non-overlapping intervals within which the frequency of observations are then calculated and plotted, the smoothed kernel density estimates the frequency of observations at different points of the distribution by averaging the frequency of observations over the moving window so that observations near the midpoint are given higher weight than the observations further from the midpoint (but still within the window). This produces a smoothed line illustrating the distribution of the variable.

Results: Data were collected at Phases 1, 3, 5, 7, and 9, with different number of participants contributing data at different study phases (**Table 1-1**). At each Phase, participants were included in the main analytic sample if they had measures of BMI and GHQ available at that phase. To be included in longitudinal analyses, each participant had to have data on BMI and GHQ at two or three consecutive study phases. **Figure 1-1** presents a flowchart de-

scribing the number of participants contributing to each sub-sample at each study phase. The first column shows the number of participants with data available for cross-sectional analysis, the second and third columns show how many participants are included and excluded from the longitudinal analyses with one and two phases of follow-up in the subsequent multilevel regression models. For models including the covariates dietary patterns, sleep duration, and SF-36 bodily pain scale, the number of participants was somewhat smaller than the main sample. Details of the numbers of participants and person-observations with full data for each covariate will be reported later when these covariates are included in the models.

Table 1-1 gives descriptive statistics for the study variables separately for each study phase. The prevalence of obesity almost tripled between Phases 1 and 9 (from 7% to 20%), although the rate of change in BMI did appear to slow down. GHQ caseness decreased by half (from 27% to 15%), with little difference in the rate of change over the study phases. The proportion of women, smokers, and low-SES participants decreased slightly. And as expected, the prevalence of longstanding illnesses increased substantially. At baseline, 24 participants had missing data on BMI and 119 participants missing data on GHQ, resulting in 10165 participants of the original 10308 Whitehall II participants at baseline. However, the maximum number of participants in the cross-sectional analyses was 10265, because 100 of the 143 participants with missing data at baseline did participate in at least one of the subsequent study phases and were therefore included in the present study in at least one of the study phases.

The statistical models were fitted in three different subsamples derived from the main sample, depending on the number of study phases used to create outcome and exposure variables. In cross-sectional analysis all participants with data on BMI and GHQ at the study phase contributed a person-observation in that Phase, so that one participant could contribute 1 to 5 person-observations for the dataset used in cross-sectional analyses.

For analyses examining changes in BMI and GHQ taking place over two study phases, participants were included if data on BMI and GHQ were available at both of these study phases, i.e., any two consecutive study phases between phases 1 and 9.

Table 1-1. Descriptive statistics of the main sample

	Phase 1	Phase 3	Phase 5	Phase 7	Phase 9
Sex (% women)	32.9/3343	30.7/2424	29.3/1600	28.9/1819	28.4/1722
Age (years)	44.4 (6.1)	49.6 (6.1)	55.7 (6.0)	61.1 (6.0)	65.8 (5.9)
BMI (kg/m2)	24.6 (3.5)	25.3 (3.7)	26.1 (3.9)	26.7 (4.3)	26.8 (4.4)
Obese (%)	7.0/710	9.6/758	14.1/770	18.8/1186	19.6/1186
Change in BMI (kg/m2)	-	0.78 (1.53)	0.90 (1.59)	0.55 (1.53)	0.08 (1.58)
GHQ score (range 30 to 120)	55.2 (10.3)	54.2 (9.8)	54.3 (10.7)	53.6 (10.8)	52.1 (9.6)
GHQ caseness (%)	27.0/2745	21.8/1723	22.1/1206	20.4/1284	15.2/919
Change in GHQ score	-	-0.89 (10.6)	0.05 (10.7)	-0.69 (10.4)	-1.22 (9.6)
Occupational grade					
Low (%)	37.4/3804	34.1/2692	30.6/1672	29.5/1857	28.1/1703
Intermediate (%)	33.2/3370	34.6/2732	36.0/1966	36.7/2313	37.2/2255
High (%)	29.4/2991	31.2/2470	33.3/1819	33.8/2133	34.7/2103
Sleep duration (range 1 to 5)	2.81 (0.79)	3.01 (0.88)	2.69 (0.88)	2.72 (0.90)	2.78 (0.92)
Bodily pain (range 0 to 9)	-	1.05 (1.24)	1.18 (1.34)	1.43 (1.38)	1.22 (1.31)
AHEI diet score (range 10 to 90)	-	50.2 (12.3)	51.4 (12.5)	51.1 (12.4)	-
Longstanding illness (%)	23.6/2397	33.8/2668	49.7/2710	60.8/3834	64.6/3915
Smoking					
No	49.4/4977	51.3/3968	52.0/2779	47.6/2858	48.5/2912
Ex-smoker	32.2/3246	34.9/2704	37.7/2017	40.4/2426	44.4/2669
Current smoker	18.4/1858	13.8/1067	10.3/548	12.0/720	7.1/427
Alcohol consumption					
None	18.1/1827	19.4/1530	15.6/841	16.8/1051	15.9/963
Moderate	66.1/6659	65.0/5129	60.6/3267	63.5/3970	62.5/3788
Heavy	15.8/1589	15.6/1228	23.8/1283	19.7/1234	21.6/1309
Physical activity (quartiles)	1.68 (1.06)	1.71 (1.07)	1.51 (1.12)	1.51 (1.12)	1.52 (1.11)
n	10165	7894	5457	6303	6061

Note: Values are percentages/numbers of participants or means (standard deviations).
N=10308 for the original Whitehall II sample.

Table 1-2. Descriptive statistics of the sample by analysis design.

	1. Cross-sectional analysis	2. Change between two study phases	3. Change over three study phases
Sex (% women)	30.4/10908	29.2/6737	29.5/3883
Age (years)	53.8 (10.0)	51.6 (8.8)	49.2 (7.5)
BMI (kg/m2)	25.7 (4.0)	26.1 (4.1)	25.1 (3.6)
Obese (%)	12.3/4610	14.4/3327	8.6/1170
GHQ score (range 30 to 120)	54.1 (10.3)	53.5 (10.1)	54.4 (10.0)
GHQ caseness (%)	22.0/7877	19.9/4599	23.5/3198
Occupational grade	0.99 (0.80)	1.03 (0.80)	1.05 (0.79)
Sleep duration (range 1 to 5)	2.81 (0.87)	2.83 (0.90)	2.85 (0.84)
Bodily pain (range 0 to 9)	1.21 (1.32)	1.19 (1.30)	1.08 (1.25)
AHEI diet score (range 10 to 90)	50.8 (12.4)	50.8 (12.4)	51.0 (12.2)
Longstanding illness (%)	43.3/15523	50.1/11556	34.0/4638
Smoking			
No	49.7/17494	50.2/11344	53.1/7132
Ex-smoker	37.1/13060	38.9/8779	35.6/4753
Current smoker	13.3/4620	10.9/2457	11.6/1555
Alcohol consumption			
None	17.7/5249	17.3/3026	15.4/2082
Moderate	64.3/19024	63.6/11128	66.4/8994
Heavy	18.0/5334	19.1/3343	18.2/2468
Physical activity (quartiles)	1.62 (1.09)	1.60 (1.10)	1.69 (1.06)
Person-observations (Persons)	35880 (10265)	23076 (8315)	13630 (5322)

Note: Values are percentages/numbers of person-observations or means (standard deviations) calculated over all the available study phases.

Each participant could thus contribute up to 4 person-observations for this dataset. Finally, for lagged change score analysis in which change in exposure over two consecutive study phases was used to predict change in the outcome between the latter phase and the phase following it (e.g., change in BMI between phases 1 and 3 predicting change in GHQ score between phases 3 and 5), all participants with data on BMI and GHQ at any three consecutive study phases were included in the dataset. Each participant therefore had the possibility of contributing up to 3 person-observations.

Table 1-2 shows the descriptive statistics for the three subsamples (means and percentages calculated over all study phases included in the respective subsample based on the multiple person-observations). There were no consistent differences in health status between the subsamples. The 3-phase longitudinal sample had lower prevalence of obesity (8.6%) than the cross-sectional sample (12.3%) and the 2-phase longitudinal sample (14.4%), presumably because obese individuals were more likely to drop out of the study over the follow-up period and thereby contributing less person-observations to the longitudinal subsamples compared to the total sample. GHQ caseness was most prevalent in the 3-phase longitudinal sample (23.5%), slightly lower in the cross-sectional sample (22.0%) and lowest in the 2-phase longitudinal sample (19.9%). The 2-phase longitudinal sample had the highest levels of longstanding illnesses (50.1%), followed by the cross-sectional sample (43.3%) and the 3-phase longitudinal sample (30.4%). The longitudinal samples were naturally also younger in terms of data cycle baseline age, because phases 7 and 9 were not included as data cycle baselines in these analyses.

Figure 1-2 plots the distributions of BMI and continuous GHQ by study phase. Over time, the distribution of BMI moved progressively to the right and became less peaked, indicating increasing mean levels of BMI during the follow-up as normal-weights tended to become overweight or obese. By contrast, the distribution of GHQ moved to the left and became more peaked, indicating decreasing levels of GHQ scores over the follow-up. **Figure 1-3** shows the corresponding distributions for change scores of BMI and GHQ between two study phases. The distribution of GHQ change became more peaked and concentrated around the value of zero with time, indicating less change in GHQ in later phases compared to earlier phases. The distribution of BMI change moved to the left, indicating progressively decelerating change in BMI.

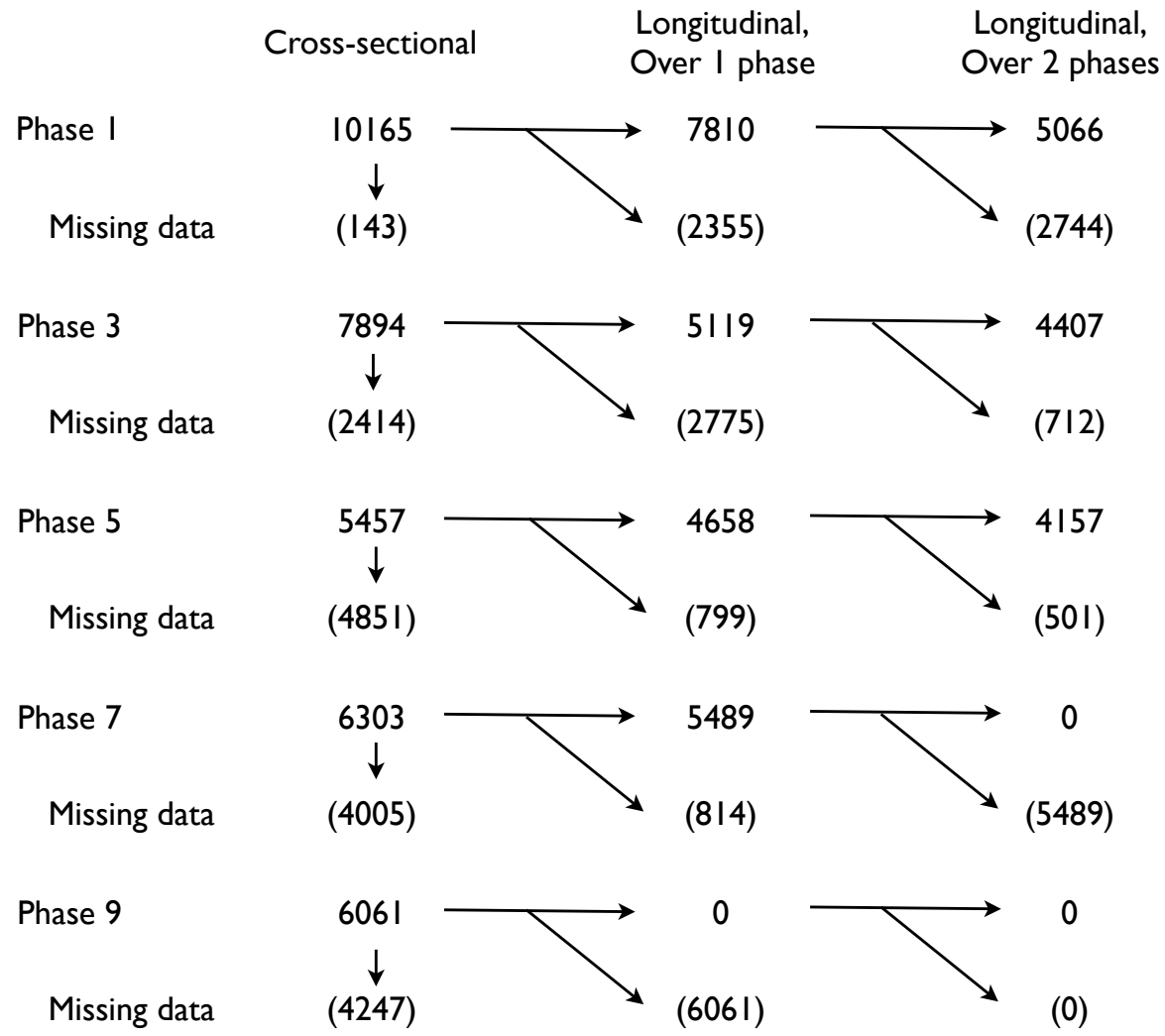


Figure 1-1. Flowchart showing the number of eligible participants in different subsamples by study phase, starting with 10308 participants (10165+143). Numbers in parenthesis indicate excluded participants. Cross-sectional analysis (first column) requires the participant to have data on BMI and GHQ in the phase in question. Longitudinal analysis (second column) over one study phases requires the participant to have data at the baseline phase of the data cycle and in the next phase. Longitudinal analysis over two study phases requires the participant to have data at the baseline phase of the data cycle, and in the next two study phases.

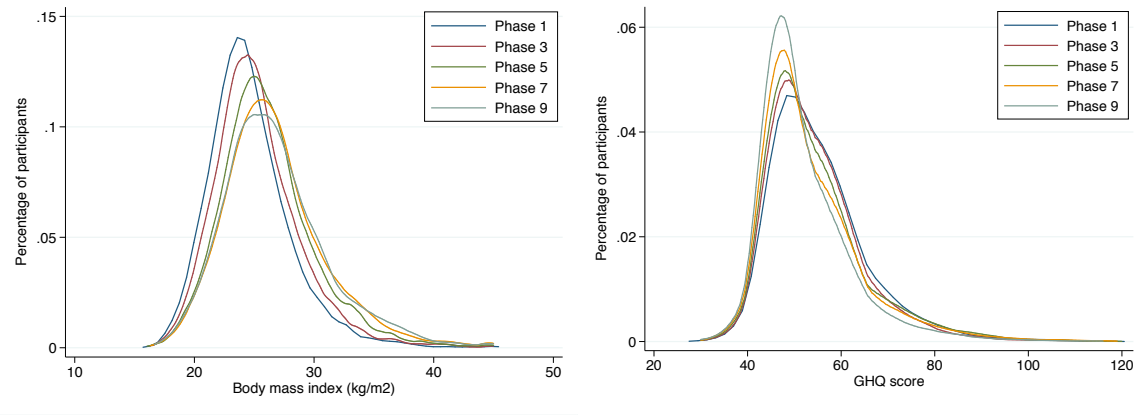


Figure 1-2. Smoothed distributions of BMI and GHQ score by study phases.

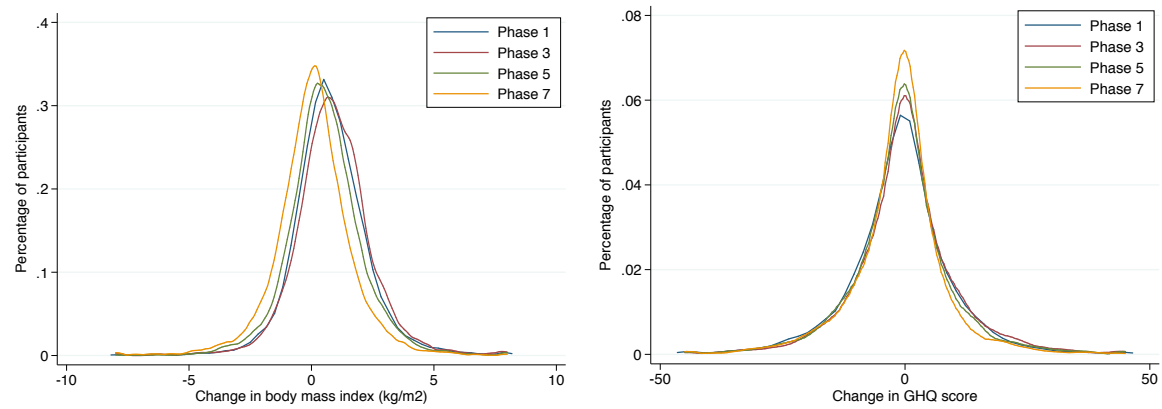


Figure 1-3. Smoothed distributions of 5-year changes in BMI and GHQ score by study phases.

Comment: These descriptive statistics provide initial contextual data for the study. Clear changes in obesity and GHQ caseness were observed over the 5 study phases, but a more substantial interpretation of these changes is postponed to a later section, which presents the results for age-related trajectories. The three subsamples used in cross-sectional and longitudinal analyses did not differ markedly from each other, although the longitudinal subsample requiring data from 3 consecutive study phases had approximately 5 percentage points lower prevalence of obesity than the cross-sectional and 2-phase longitudinal

samples. Perhaps surprisingly, the 3-phase longitudinal sample also had the highest levels of GHQ caseness (23.5%) compared to the two other subsamples (22.0% and 19.9%), suggesting that the 3-phase longitudinal sample was not consistently healthier than the 2-phase longitudinal and cross-sectional subsamples; general expectation of poor health affecting selective drop-out might lead one to expect otherwise. Selective attrition is investigated in detail in the next section.

7.2. Attrition

Purpose: In multilevel modeling, participants can have missing data in some of the measurement time points, which allows one to include in the analysis all participants with data from at least one measurement time. Thus, the total sample includes individuals with different participation and attrition patterns. The present section describes the attrition patterns over the 5 study phases and examines how the study covariates are related to selective attrition. In addition to providing descriptive statistics of selective attrition, an attrition indicator variable is created for each participant to take into account selective attrition (and the unobserved characteristics affecting participants' likelihood of staying in the study over the follow-up period) in subsequent longitudinal analysis.

Methods: Attrition analysis was carried out in four steps. First, the frequency of different patterns of study participation (or, to be precise, the availability of data for BMI and GHQ) over the 5 study phases was determined to provide a summary of all the different alternative combinations of data availability for the participants over measurement times. Second, the participants were categorized according to the length of follow-up (the most recent study phase in which they had taken part in), and descriptive statistics of the study variables were calculated separately in each of these groups to evaluate sample differences as a function of length of follow-up. Third, logistic regression analysis was used to predict the probability of non-participation in the next phase as a function of study covariates at each study phase. Finally, following the method of pattern mixture modeling,[348] a new variable characterizing selective attrition for each participant was created.

Results: All the 31 alternative combinations of study participation, defined as the availability of data on BMI and GHQ, in the 5 study phases are shown in **Table 2-1**. Full data at each of the study phases was the most common pattern (38.1% of participants), followed

Table 2-1. Participation patterns with each row representing a specific combination of participation and non-participation, listed in order of descending frequency

	Study phase participation (X = Yes; . = No)					Participants	
	Phase 1	Phase 3	Phase 5	Phase 7	Phase 9	%	n
1	X	X	X	X	X	38.1	3906
2	X	.	.	.	.	16.2	1665
3	X	X	.	.	.	11.3	1157
4	X	X	.	X	X	11.0	1131
5	X	X	X	.	.	4.8	490
6	X	X	X	X		4.4	455
7	X	X	.	X	.	2.3	236
8	X	X	.	.	X	2.1	220
9	X	X	X	.	X	2.1	215
10	X	.	X	X	X	2.0	204
11	X	.	.	X	X	1.8	184
12	X	.	.	.	X	1.0	104
13	X	.	.	X	.	0.7	74
14	X	.	X	.	.	0.6	57
15	.	X	X	X	X	0.4	41
16	X	.	X	X	.	0.4	40
17	X	.	X	.	X	0.3	26
18	.	X	.	X	X	0.2	15
19	.	X	.	.	.	0.1	14
20	.	.	X	X	X	0.1	6
21	.	X	X	.	.	0.1	5
22	.	X	X	X	.	0.1	5
23	.	.	.	X	.	0.0	2
24	.	.	.	X	X	0.0	2
25	.	.	X	.	.	0.0	2
26	.	.	X	.	X	0.0	2
27	.	X	X	.	X	0.0	2
28	.	.	.	.	X	0.0	1
29	.	.	X	X	.	0.0	1
30	.	X	.	.	X	0.0	1
31	.	X	.	X	.	0.0	1
Total						100.0	10265

Note: Study participation is here defined as the availability of data on BMI and GHQ.

by drop out after phase 1 (16.2%), full data in phases 1 and 3 but drop out after phase 3 (11.3%), otherwise full data except missing data in phase 5 (11.0%), full data up to phase 5 (4.8%), and full data up to phase 7 (4.4%). These 6 participation patterns accounted for 85.8% of all the alternative participation patterns of the participants, with the remaining 14.2% of the participants having more checkered participation/non-participation patterns.

The length of follow-up period is an important indicator of attrition when considering longitudinal data. In **Table 2-2**, baseline characteristics are presented separately for groups of participants who dropped out of the study at different points in time. For instance, 1663 participants took part at baseline but at none of the following phases, while 5998 participants were followed up to phase 9. Participants who were followed up to phase 9 were more likely to be men, younger, non-obese, and to have higher occupational grade, lower prevalence of longstanding illnesses, and lower SF-36 bodily pain score than those dropping out of the study earlier on. By contrast, the differences in GHQ score or GHQ caseness were small; participants followed up to phase 9 were actually slightly more likely to be GHQ cases than those dropping out of the study after baseline (27.9% vs. 24.8%).

Table 2-3 extends the study of attrition patterns by assessing sex- and age-adjusted associations between study covariates and the probability of non-participation in the next phase separately for phases 1 to 7. Females, smokers, obese individuals, and those with low occupational grade, high SF-36 bodily pain score were fairly consistently more likely to drop out of the study. Age, GHQ score, poorer diet (AHEI score), and low physical activity became stronger predictors of non-participation over time. For instance, GHQ caseness was not related to attrition between Phases 1 and 3 (OR=0.93) but did predict drop out between Phases 7 and 9 (OR=1.28).

Selective attrition may introduce bias in the estimated associations in longitudinal studies, and several methods to adjust for selective attrition have been suggested. In the present study, the method of pattern mixture modeling developed for multilevel regression

Table 2-2. Baseline characteristics according to attrition pattern indicator (the phase in which the participant most recently provided data on BMI and GHQ).

	The most recent study phase for which data for the participant were available				
	Phase 1	Phase 3	Phase 5	Phase 7	Phase 9
Sex (% women)	45.0/748	36.5/421	33.8/185	36.5/292	29.3/1697
Age (years)	45.2 (6.2)	45.4 (6.1)	46.3 (6.2)	45.6 (6.2)	43.7 (5.9)
BMI (kg/m2)	25.1 (4.0)	24.8 (3.6)	25.0 (3.6)	25.2 (3.7)	24.4 (3.2)
Obese (%)	11.4/189	7.6/88	7.5/41	9.7/78	5.2/314
GHQ score (range 30 to 120)	55.2 (10.9)	54.8 (10.5)	55.4 (11.1)	55.4 (10.1)	55.3 (10.1)
GHQ caseness (%)	24.8/412	25.8/298	26.1/143	27.6/221	27.9/1671
Occupational grade (0 to 2)	0.64 (0.79)	0.70 (0.80)	0.80 (0.83)	0.80 (0.81)	1.07 (0.79)
Sleep duration (range 1 to 5)	2.81 (0.85)	2.79 (0.79)	2.73 (0.85)	2.79 (0.80)	2.83 (0.77)
Bodily pain (range 0 to 9)*	-	1.20 (1.41)	1.08 (1.31)	1.10 (1.23)	1.02 (1.22)
AHEI diet score (range 10 to 90)*	-	49.0 (12.8)	49.3 (12.9)	49.1 (13.0)	50.6 (12.0)
Longstanding illness (%)	25.6/425	25.2/291	27.0/148	26.0/208	22.1/1325
Smoking					
No	43.0/725	44.9/518	48.4/266	43.7/352	53.1/3201
Ex-smoker	27.1/457	31.6/364	29.3/161	34.5/278	33.4/2014
Current smoker	29.9/504	23.5/271	22.4/123	21.8/176	13.4/809
Alcohol consumption					
None	25.6/430	24.4/285	22.0/120	20.0/161	14.6/877
Moderate	59.7/1002	60.6/706	61.7/337	63.1/507	69.6/4187
Heavy	14.7/246	15.0/175	16.3/89	16.9/136	15.9/956
Physical activity (quartiles)	1.54 (1.10)	1.53 (1.11)	1.56 (1.08)	1.60 (1.07)	1.76 (1.02)
n	1663	1155	548	801	5998

Note: Values are percentages/numbers of participants or means (standard deviations)

Baseline characteristics assessed at Phase 1 unless otherwise indicated.

* Baseline characteristics assessed at Phase 3.

models[348] was applied to take into account that the participants did not drop out of the study randomly. In pattern mixture modeling, a covariate characterizing the participants' drop-out patterns is created, and this covariate is included in the multilevel regression models to take into account differences between groups with different drop-out patterns. There are many

alternative ways to create the drop-out indicator, e.g., based on the number of follow-ups the participant takes part in, the final follow-up phase at which the participant provides data, or a more detailed structure of drop-out and participation over the study phases. The researcher needs to decide what kind of drop-out patterns are taken into account.

Table 2-1 suggested that most of the variance in drop-out patterns was related to the most recent study phase in which the participant provided data on BMI and GHQ. The value of the attrition indicator for each participant was therefore determined by the most recent study phase (0=drop-out after phase 1; 4=participated in phase 9). The number of participants in each group is shown on the bottom row of **Table 2-2**.

Table 2-3. Predicting non-participation in the next study phase by covariates in the preceding study phase (odds ratios)

	Phase 1	Phase 3	Phase 5	Phase 7
Sex (0=male, 1=female)	**1.55**	**1.25**	**1.37**	**1.52**
Age (per 5 years)	**1.05**	**1.09**	**1.22**	**1.36**
BMI (per kg/m2)	**1.04**	**1.02**	**1.03**	**1.04**
Obesity	**1.73**	**1.37**	**1.24**	**1.49**
GHQ score (per 10 points)	0.99	1.04	**1.10**	**1.19**
GHQ caseness	0.93	1.11	**1.20**	**1.28**
Occupational grade	**0.74**	**0.79**	**0.71**	**0.69**
Sleep duration	1.02	0.98	**0.86**	0.97
Bodily pain (SF-35)	**1.15**	**1.06**	**1.07**	**1.09**
AHEI score	1.00	**1.00**	**0.99**	**0.98**
Longstanding illness	**1.14**	1.03	**0.75**	**1.17**
Smoking (0=no, 1=yes)	**2.05**	**1.47**	**2.09**	**2.07**
Physical activity (quartiles)	0.96	**0.92**	**0.81**	**0.79**
Alcohol consumption (0=none/ moderate, 1=heavy)	1.05	1.00	1.00	0.96
Number of participants	10165	7894	5457	6303
Percentage/number of participants with missing data at the next phase	23.2/2355	35.2/2775	14.6/799	12.9/814

All associations adjusted for age and sex.

Odds ratios printed in bold are statistically significant ($p<0.05$)

Comment: Attrition analysis demonstrated clear and consistent associations between study variables and selective attrition. First, attrition was related to health status and health behaviors, so that longer follow-up time was predicted by being non-obese, low bodily pain, non-smoking, healthy diet, and high physical activity. GHQ caseness increased the risk of attrition only after phase 5, and the overall differences in GHQ caseness between participants dropping out of the study in different study phases were modest. Somewhat surprisingly, participants who were still in the study in phase 9 had slightly higher rather than lower prevalence of GHQ caseness at baseline than those who left the study after baseline (27.9% vs. 24.8%), suggesting relatively weak effect of GHQ caseness on selective attrition compared to many other covariates, such as smoking or occupational grade.

Multilevel modeling of longitudinal data differs from many of the earlier longitudinal analysis methods, such as repeated-measure analysis of variance, which required complete data from all the measurement time points for the participant in order for the participant to be included in the analysis.[341] Multilevel regression does not require complete data from all measurement points but uses all the available data from each participant. Even data from individuals with only one measurement time are included – they contribute to the estimation of mean level (i.e., intercept) and between-individual variance but not to estimation of change over time (i.e., slope) and within-individual variance. This does not yet solve the problem of attrition, but it does mitigate the need to apply data imputation methods in order not to lose participants with incomplete repeated-measurement data.

Although multilevel regression does not impute any missing values, the maximum likelihood estimation produces valid inferences in the presence of "ignorable nonreponse".[348] That is, the estimation is not biased by missing data if (a) the patterns of missing data are unrelated to any of the variables included in the analysis (missing completely at random), or (b) the probability of nonreponse is dependent on observed covariates included in the model

and previous values of the dependent variable from the participants with missing data (missing at random). Thus, the estimation of the present models takes into account the selective attrition related to obesity and CMDs and other covariates included in the models (**Table 2-3**). Pattern mixture modeling extends the missing data treatment by introducing a new variable that provides information on the missing pattern itself. The missing data mechanisms therefore does not need to be ignorable, because the attrition indicator provides information for the purpose of missing at random estimation.[348]

The issue of missing data cannot be solved completely with any statistical method, so a variety of methodological approaches have been suggested to address attrition in longitudinal analysis. Alternatives to pattern mixture modeling include "selection models" or "joint modeling" of the outcome and drop-out, in which a model of attrition probability is first developed and then the drop-out propensity scores are used to adjust the main analysis for drop-our propensity.[349] The advantage of pattern mixture modeling compared to selection models is that attrition can be modeled without measured predictors of attrition probability. Another modern method to tackle missing data is multiple imputation.[350] Given that multilevel regression can already include participants without complete data and provide valid inferences if the data are not missing not at random, multiple imputation does not substantially add value in the context of multilevel regression.

The main limitation of pattern mixture modeling compared to selection models (i.e., first building a model to predict drop-our probability and then adjusting for this probability in the main analysis) is that the pattern mixture model indicator is not effective when there is no variance in the attrition indicator variable. For example, when using obesity at baseline to predict CMDs 20 year later (see section 7.5.), only individuals who have been followed up to the last study phase are included, and they all get the same value on the attrition indicator indicating the length of the participant's follow-up time. Also, the attrition indicator does

not take into account different reasons for attrition (e.g., death, inability to participate, refusal, relocation), which may be important in some instances.

7.3. Age trajectories of BMI and GHQ

Purpose: The current section examines how BMI and GHQ develop with age, both between and within individuals.

Methods: Multilevel linear regression was used to model age-related changes in 1) BMI, 2) obesity, and 3) within-individual 5-year change scores of BMI. Corresponding models were fitted for GHQ, GHQ caseness, and GHQ change scores. In order not to force the functional form of the age trajectories to any predefined shape (linear, quadratic, or any other), age was used as a categorical variable (coded in years). All models were adjusted for sex, birth year (birth cohort effect), and attrition indicator. The specific role of adjustments for birth year and attrition was examined by comparing the age trajectories unadjusted and adjusted for these covariates.

Results: In a multilevel linear regression model with no covariates, the intraclass correlation for BMI was 0.80, indicating that a substantial proportion of total sample variance in BMI (80%) was due to between-individual differences in mean levels of BMI averaged across study phases. The remaining 20% of the total variance was due to within-individual variation around the participants' mean levels of BMI over the study phases. Intraclass correlation for GHQ was 0.43, suggesting higher within-individual variation in GHQ compared to BMI. That is, 43% of the total variance in continuous GHQ was due to average differences between individuals while 57% of the variance was due to within-individual variation around the individuals' average GHQ levels across study phases.

Figure 3-1 plots the age-, sex- and attrition-adjusted mean levels of BMI, prevalence of obesity, and BMI change over 5-year periods, respectively, against age. Mean BMI and obesity prevalence increased substantially and fairly linearly between ages 35 and 80, with

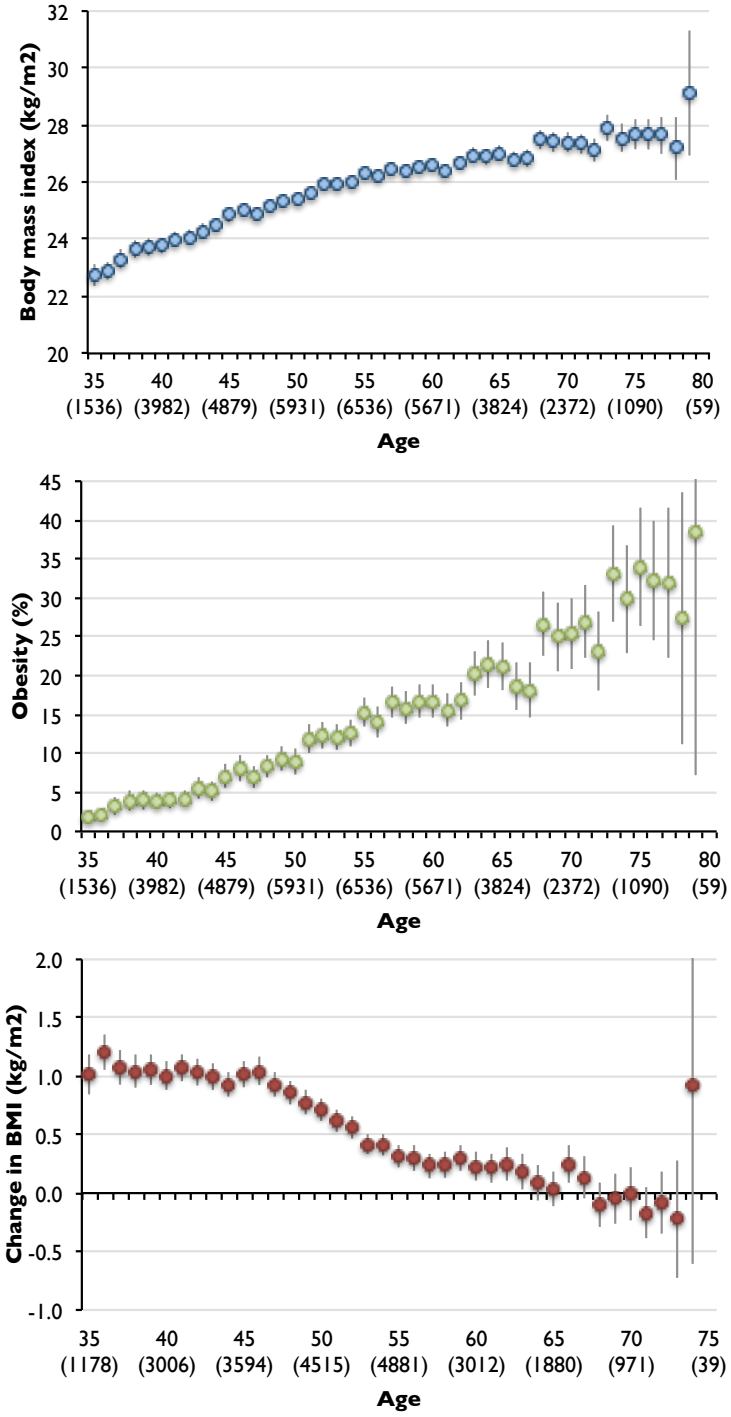


Figure 3-1. Mean body mass index, obesity prevalence, and 5-year change in BMI plotted against age, adjusted for sex, birth year, and attrition indicator.

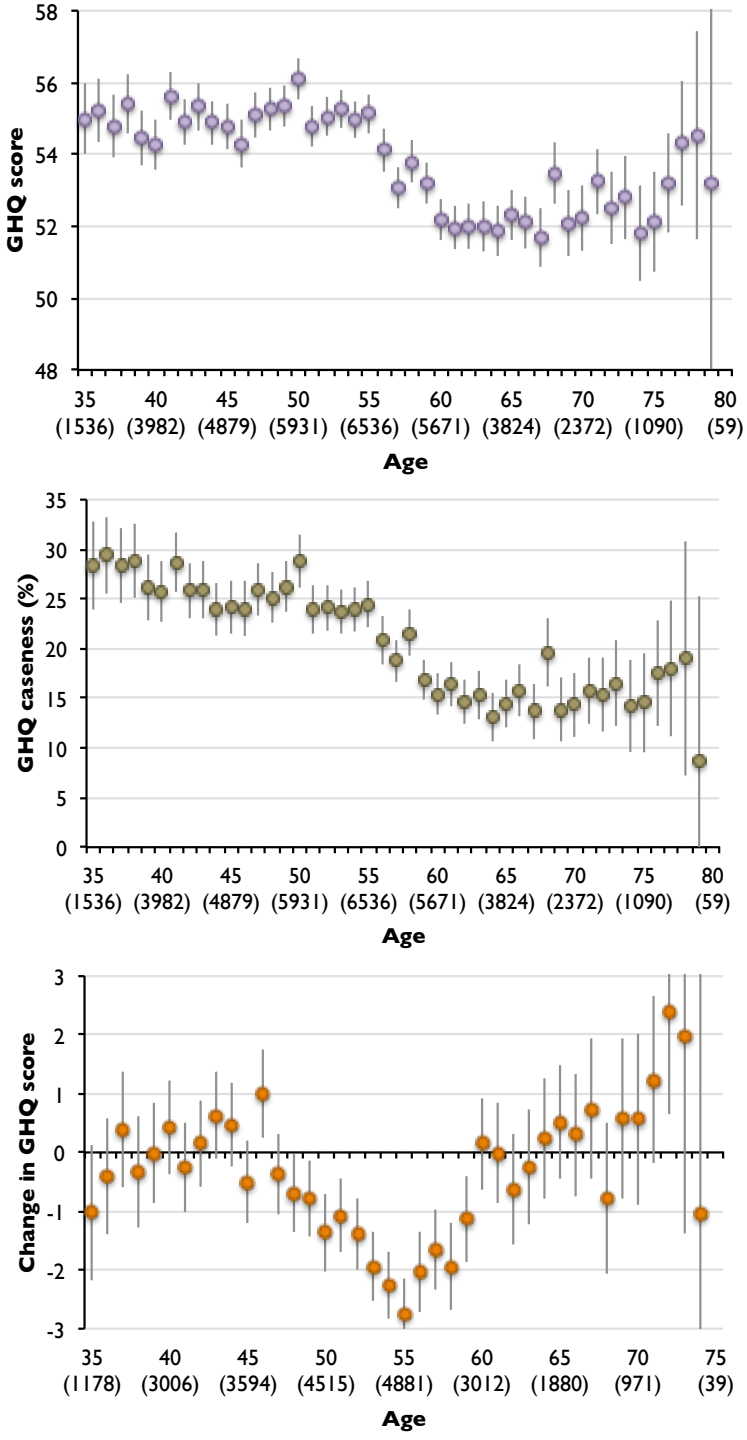


Figure 3-2. Mean GHQ score, GHQ caseness prevalence, and 5-year change in GHQ plotted against age, adjusted for sex, birth year, and attrition indicator.

<5% of participants under 40 years of age being obese compared to >25% of obese participants among participants over 70 years. However, as suggested by the decelerating increase of average BMI levels (top panel of **Figure 3-1**), the rate of within-individual increase in BMI attenuated over time from a relatively stable +1 BMI units per 5 years between ages 35 and 45 to null or even slightly negative by age 65 (bottom panel of **Figure 3-1**).

Figure 3-2 plots the corresponding age trajectories for GHQ. GHQ levels remained quite stable between ages 35 and 55, after which there was a decline in GHQ scores and GHQ caseness continuing up to age 65. Between ages 65 and 75, GHQ again remained quite stable. After age 75 there was some indication of increasing GHQ scores, but due to low number of participants over age 75, the estimates were too imprecise to make strong conclusions on increasing GHQ in old age. Age-related patterns in within-individual changes over 5-year periods provided very similar conclusions: There was little change between ages 35 and 45, accelerating decrease in GHQ between ages 45 and 55, followed by a return to stable GHQ change between ages 55 and 65, after which there was suggestive evidence for increasing GHQ scores after age 70. However, the estimates were again too imprecise to draw definitive conclusions of within-individual GHQ change in old age.

Age trajectories in **Figure 3-1** and **Figure 3-2** were adjusted for sex, attrition, and birth year. To examine the influence of selective attrition and birth cohort effects on the estimated age trajectories of obesity and GHQ caseness, the models were fitted without adjustment for attrition and for birth year (**Figure 3-3**). Adjusting for attrition (the most recent follow-up in which the participant had provided data on BMI and GHQ) had little effect on the age trajectories, as indicated by the almost completely overlapping estimates with unadjusted means in **Figure 3-3**.

By contrast, adjusting for birth cohort effects had a substantial influence on the shape of obesity trajectory, so that the unadjusted increase in obesity begun to flatten out around age 60-65 whereas the age trajectory adjusted for birth year continued to increase linearly

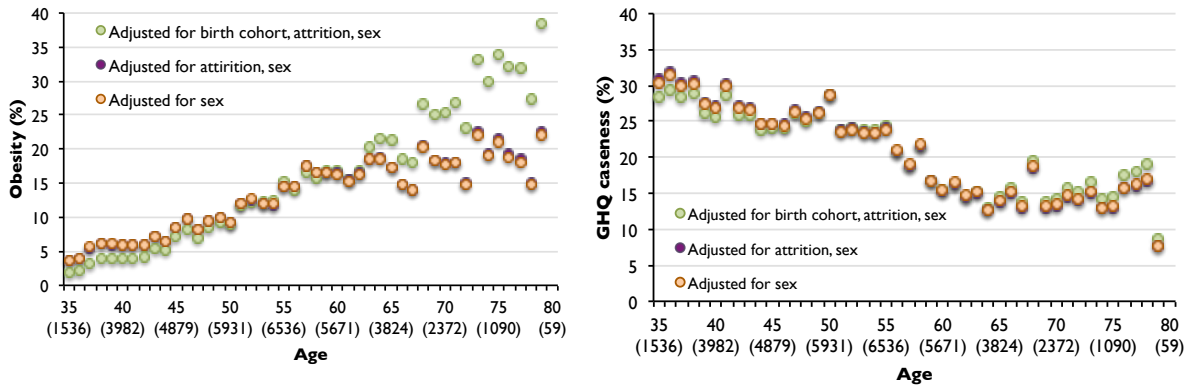


Figure 3-3. Illustrating the effect of adjusting for birth cohort effects when assessing age trajectories in obesity and GHQ caseness prevalence. Predicted values of models adjusted for attrition and sex (in dark red) are plotted in the figures, but they almost completely overlap with predicted values of models adjusted only for sex (in orange).

even after age 65. The cohort effect was due to the fact that data for old age was derived from older cohorts who had lower prevalence of obesity than younger cohorts. Given that the cohort effects in obesity were not the main focus here, they are only briefly illustrated here. The participants were born between years 1930 and 1953. When birth year was categorized into 5-year intervals (1930-4, 1935-9, 1940-4, 1945-9, 1950-3), data for BMI were available for all birth cohort groups between ages 52 and 62 from different study phases. Within this age range, the prevalence of obesity from the oldest to the youngest birth cohort group was 9.8%, 12.0%, 16.0%, 18.9%, and 19.6%, suggesting a two-fold difference in obesity at age 52-62 between the youngest (1950-3) and oldest (1930-4) birth cohort.

Comment: Mean BMI and prevalence of obesity increased with age, although the average rate of within-individual increase in BMI over time decelerated with age; between ages 35 and 45 the participants gained an average of 1 BMI unit per 5 years, but after reaching age 65 the average within-individual change in BMI was not distinguishable from zero. The estimation of obesity prevalence by age was substantially affected by adjustment for

birth cohort effects, because older cohorts had lower prevalence of obesity and the data for older ages in the age trajectory modeling was naturally derived from the older birth cohorts. When birth cohort effects were not taken into account, the increase in obesity appeared to slow down around age 60-65. But when the lower obesity prevalence in older cohorts was taken into account in modeling the age trajectory, obesity continued to increase also after age 65. Thus, despite the observation of decelerating within-individual change in BMI, the prevalence of obesity was estimated to increase with age more steeply after age 65 than the crude data not taking into account birth cohort differences would have suggested.

GHQ exhibited a non-linear developmental trajectory characterized by a temporary improvement in GHQ scores between ages 45 and 60, with a peak at age 55, as suggested by the within-individual change scores. GHQ caseness prevalence remained fairly stable between ages 35 and 55, after which it decreased up to age 70. There was suggestive evidence for increasing GHQ in old age, but the data did not allow one to draw strong conclusions to be drawn about this late development. The age trajectory for GHQ caseness was not substantially influenced by birth cohort or attrition effects.

7.4. Cumulative development of obesity and GHQ

Purpose: The preceding section assessed how obesity and GHQ caseness develop with age. The present section examines the cumulative development of these outcomes with time, i.e., how obesity status or GHQ caseness in a given study phase is dependent on obesity status and GHQ caseness 1) in one of the previous study phase, and 2) in all the previous study phases.

Methods: First, transition matrices of obesity status between two study phases with 5-, 10-, 15-, and 20-year follow-up intervals are calculated. These transition matrices indicate the proportion of non-obese individuals who became obese, and vice versa, during the follow-up period, and the proportion of obese and non-obese individuals who retain the same obesity status over time. Second, the cumulative risk of obesity is modeled as a function of the number of times the individual has been obese at previous measurement phases. For each phase, a cumulative obesity score is calculated as a sum of the times the person has been obese in the previous study phases, and this cumulative score is used to predict the probability of being obese in the study phase. A corresponding analysis is carried out for GHQ caseness. The analysis is performed with multilevel logistic regression in which a participant can contribute 1 to 4 person-observations of the cumulative exposure between phases 1 and 7, depending on the number of consecutive study phases uninterrupted by non-participation after Phase 1. In other words, the calcuation of the cumulative exposure score for a give study phase requires there to be no missing data in the exposure variable at any of the phases preceding the given study phase. For instance, a participant with missing data on obesity at phase 5 would contribute 1 person-observation for the analysis: obesity at phase 1 predicting phase 3 obesity; cumulative score across phases 1, 3, 5, and 7 would not be calcu-

lated even if the participant had full data on obesity at all other phases except phase 5 because of the missing data at phase 5.

Results: The transition probabilities of obesity status over 5 to 20 years of follow-up are shown in **Table 4-1**. The risk of becoming obese increased with increasing length of follow-up interval. Over 5 years, 5.5% of non-obese participants became obese, while this proportion was 15.8% at the 20-year follow-up. The reverse transition was less strongly associated with length of follow-up. While 12.8% of obese participants were non-obese after 5 years of follow-up, the proportion was 9.5% over a 20-year interval. The transition probability for GHQ non-cases becoming GHQ cases remained fairly stable (between 10.8% and 13.9%) over 5 to 20 years of follow-up (**Table 4-2**).

Table 4-1. Transition matrices of obesity status with different follow-up intervals.

	Obesity status at data cycle baseline	
	Non-obese; % (n)	Obese; % (n)
Over 5 years		
Non-obese	94.5 (19849)	12.8 (332)
Obese	5.5 (1162)	87.3 (2271)
Total	100.0 (21011)	100.0 (2603)
Over 10 years		
Non-obese	90.0 (13114)	12.3 (176)
Obese	10.0 (1457)	87.7 (1254)
Total	100.0 (14571)	100.0 (1430)
Over 15 years		
Non-obese	86.3 (9629)	9.9 (83)
Obese	13.7 (1532)	90.1 (756)
Total	100.0 (11161)	100.0 (839)
Over 20 years		
Non-obese	84.3 (4874)	9.5 (31)
Obese	15.8 (911)	90.5 (294)
Total	100.0 (5785)	100.0 (325)

Values are percentages (and numbers of person-observations in parenthesis). Transition probabilities are calculated over 5 study phases with 5-year intervals, so transitions over shorter follow-up times are calculated with larger samples than transitions over longer follow-up times.

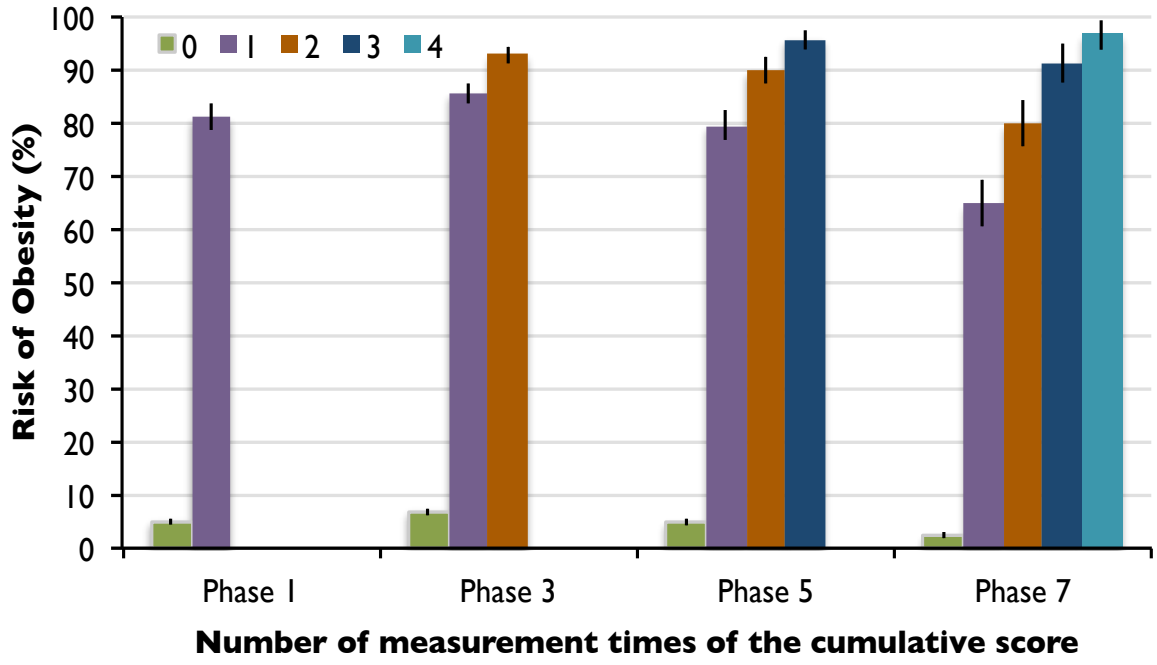
Table 4-2. Transition matrices of GHQ caseness with different follow-up intervals

	GHQ caseness at data cycle baseline	
	Non-Case; % (n)	Case; % (n)
Over 5 years		
Non-Case	86.1 (16648)	59.0 (3439)
Case	13.9 (2691)	41.0 (2389)
Total	100.0 (19339)	100.0 (5828)
Over 10 years		
Non-Case	86.1 (11544)	62.6 (2686)
Case	13.9 (1870)	37.4 (1603)
Total	100.0 (13414)	100.0 (4289)
Over 15 years		
Non-Case	86.9 (8181)	67.7 (2148)
Case	13.1 (1230)	32.3 (1026)
Total	100.0 (9411)	100.0 (3174)
Over 20 years		
Non-Case	89.2 (4163)	73.2 (1342)
Case	10.8 (504)	26.8 (491)
Total	100.0 (4667)	100.0 (1833)

Values are percentages (and numbers of person-observations in parenthesis). Transition probabilities are calculated over 5 study phases with 5-year intervals, so transitions over shorter follow-up times are calculated with larger samples than transitions over longer follow-up times.

By contrast, the risk of GHQ case remaining a GHQ case after 5, 10, 15, and 20 years of follow-up decreased from 41.0% to 26.8%.

Figure 4-1 shows how the cumulative obesity score predicted the probability of obesity at the next phase. Participants who had not been obese up to a given phase had approximately 5% risk of becoming obese at the next phase after 5 years. Having been obese at least in one previous study phase predicted a >60% probability of being obese in the future, and this probability increased linearly with the number of measurement times in which the participant had been obese, the probability reaching >90% if the participant had been obese at least two previous study phases and 97% if the participant had been obese at all four measurement times between phases 1 and 7.



Cumulative obesity score		Phase 1	Phase 3	Phase 5	Phase 7	Phase 9
	0	93.0/9455	89.6/7064	84.7/4364	80.1/3671	77.8/3229
	1	7.0/710	5.2/410	6.8/350	6.4/294	5.2/217
	2	-	5.2/407	4.3/221	6.0/273	4.9/202
	3	-	-	4.2/218	3.6/164	5.3/218
	4	-	-	-	3.9/179	3.5/145
	5	-	-	-	-	3.4/140
Total n		10165	7881	5153	4581	4151

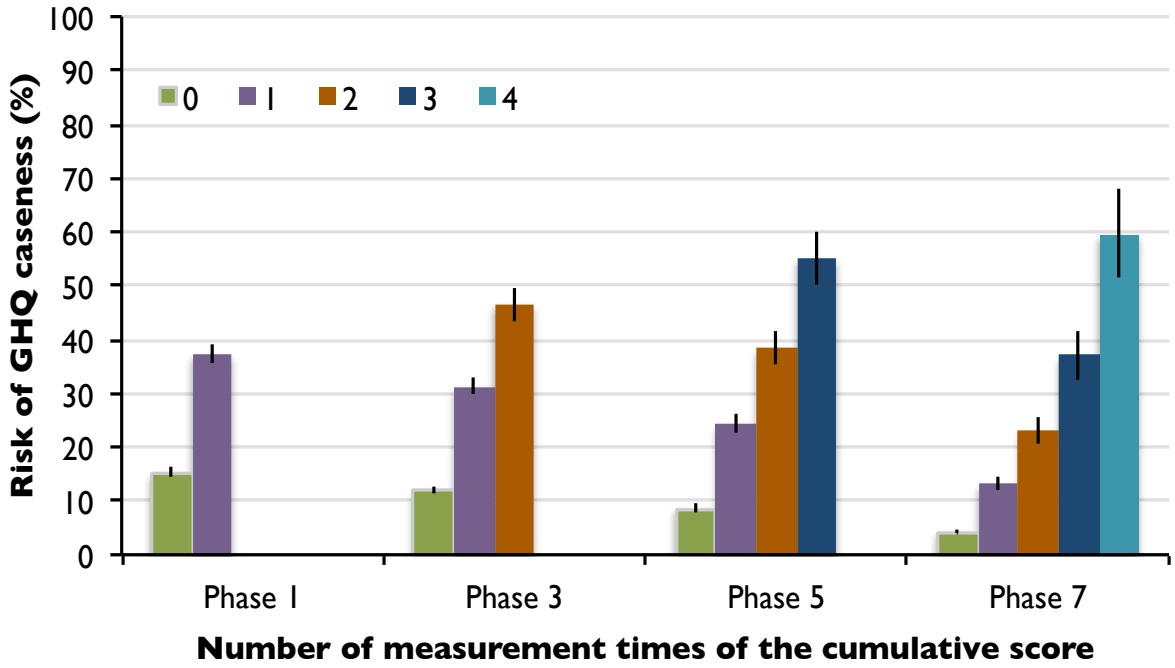
Percentage/Number of participants by cumulative obesity score and study phase

Notice that data from Phase 9 are not used in the analysis illustrated in the figure because no data are available for obesity in the next phase (future phase 11).

Figure 4-1. Risk of obesity at the subsequent study phase as a function of number of times the person has been obese up to the previous study phase, adjusted for sex, birth year, and attrition indicator.

Figure 4-2 shows the cumulative analysis for GHQ caseness. The pattern suggested a progressively increasing risk of GHQ caseness as a function of the number of times the parti-

cipant had been a GHQ case at previous study phases. At phase 7, a participant who had not been a GHQ case at any of the 4 previous measurement times had a 4% probability of being



Cumulative GHQ score		Phase 1	Phase 3	Phase 5	Phase 7	Phase 9
	0	73.0/7420	61.7/4830	54.4/2835	48.6/2666	45.9/2267
	1	27.0/2745	27.4/2141	26.4/1377	26.2/1436	25.4/1255
	2	-	10.9/852	13.4/699	14.2/779	14.3/707
	3	-	-	5.8/301	7.5/414	7.9/391
	4	-	-	-	3.5/194	4.3/212
	5	-	-	-	-	2.2/108
Total n		10165	7881	5153	4581	4151

Percentage/Number of participants by cumulative obesity score and study phase

Notice that data from Phase 9 are not used in the analysis illustrated in the figure because data for GHQ caseness at the next phase (future phase 11) are not available.

Figure 4-2. Risk of GHQ caseness at the subsequent study phase as a function of number of times the person has been a GHQ case up to the previous study phase, adjusted for sex, birth year and attrition indicator.

a GHQ case in phase 9 compared to a 60% risk for a participant who had been a GHQ case at all of the 4 preceding phases. The tables below **Figure 4-1** and **Figure 4-2** show the number of participants in each group separately by study phase. Naturally, the range of the cumulative score was limited by the number of times obesity and GHQ caseness had been measured. The total number of participants decreased at each study phase because the cumulative score could only be calculated for participants having complete data for the exposure variable up to the given phase.

Comment: These data demonstrate strong path dependence in the development of obesity and GHQ caseness. The risk of non-obese participants becoming obese increased with time from 5.5% to 15.8% when examined after 5 to 20 years of follow-up, while obesity at one phase was quite similarly related to future obesity risk whether future obesity was measured 5 or 20 years later, future risk being between 87.3% and 90.5%. The future risk of obesity also increased linearly with the number of times the person had been obese at previous study phases. For GHQ caseness, the probability of transition from GHQ caseness to non-caseness increased with time while the probability of crossing the threshold of GHQ caseness remained relatively stable between 5 and 20 years of follow-up for GHQ non-cases. GHQ caseness also increased linearly with the number of times the person had been a GHQ case at previous study phases, although this cumulative risk was not as strong as it was for obesity.

7.5. Associations between baseline obesity at phase 1 and GHQ caseness at phases 1 to 9

Purpose: Obesity may be differently related to GHQ caseness when assessed cross-sectionally vs. longitudinally, and the strength of the longitudinal association may vary depending on the length of the follow-up. This section examines the cross-sectional and longitudinal associations of baseline obesity with GHQ caseness assessed at phases 1 to 9.

Methods: Cross-sectional and longitudinal associations are assessed with 5 separate linear regression models for each of the study phases. In addition to the models adjusted for sex and age, additional longitudinal models with adjustment for baseline GHQ caseness are fitted. Due to selective attrition over the follow-up period, the sample composition of different study phases is not the same, which can introduce variability in the strength of the estimated longitudinal associations even if the true associations remained the same over the follow-up. To exclude this possibility, the cross-sectional and longitudinal models are additionally fitted in participants who have full data in all the study phases (n=3906) to keep the sample composition the same. To statistically test whether the association between obesity and GHQ caseness is different in those with vs. those without full data, a dichotomous variable for each participant is created to indicate whether or not the participant has full data, and then the interaction effect between this indicator variable and obesity is tested in each of the models. A significant interaction effect would indicate that the association between obesity and GHQ caseness is stronger or weaker in those with compared to those with no full data over all the study phases.

Table 5-1. Separate logistic regression models for associations of baseline (phase 1) obesity with GHQ caseness in phases 1 to 9.

Outcome	Model 1: Unadjusted for baseline GHQ	Model 2: Adjusted for baseline GHQ	Model 3: Model 1 fitted in participants with full data	p for difference between Models 1 and 3	n
GHQ caseness in					
Phase 1	1.10 (0.93, 1.31)	-	1.14 (0.82, 1.58)	0.697	10165
Phase 3	1.04 (0.83, 1.31)	1.04 (0.82, 1.32)	1.33 (0.94, 1.87)	0.039	7881
Phase 5	1.35 (1.03, 1.77)	1.35 (1.02, 1.79)	1.28 (0.90, 1.81)	0.745	5446
Phase 7	1.46 (1.14, 1.87)	1.49 (1.16, 1.93)	1.20 (0.83, 1.72)	0.174	6293
Phase 9	1.48 (1.12, 1.97)	1.50 (1.13, 2.01)	1.30 (0.88, 1.92)	0.341	6053

All models are adjusted for sex, age, and attrition indicator.

Models 1 are fitted in samples with maximum number of participants (numbers in the far right-hand column)

Models 2 are models 1, adjusted for baseline GHQ caseness

Models 3 are fitted in participants with full data available at each phase (n=3906)

p-value indicates the difference in the association between those without full data vs. those with full data (model 1 vs. model 3)

Results: Baseline obesity was not related to baseline GHQ (OR=1.10) or with GHQ at the next phase (OR=1.04; **Table 5-1, Model 1**). However, a significant association emerged for phases 5 to 9 (ORs between 1.35 and 1.48), suggesting that the association strengthened with lengthening follow-up time. Adjusting for baseline GHQ caseness did not alter the coefficients substantially (**Table 5-1, Model 2**), and the observed changes in phases 7 and 9 indicated small increase rather than decrease in the odds ratios when adjusted for baseline GHQ caseness.

When the models were fitted in the 3906 participants with full data at all the study phases, there was little change in the cross-sectional association but the different longitudinal associations were all quite similar in magnitude, although not statistically significant due to the diminished sample size, with no evidence of a strengthening association with longer follow-up times. The latter result suggests that the strengthening association observed in

Model 1 may have been due to effects of attrition. Interaction effects between obesity and the indicator variable of 'full data vs. without full data' suggested no consistent effect of study attrition on the coefficients. At phase 3, the association was significantly stronger among those with full data compared to those without full data (p=0.039) but neither of the coefficients themselves were statistically significant.

Comment: In standard logistic regression models, obesity was not significantly related to GHQ caseness risk cross-sectionally or over 5 years follow-up but, surprisingly, a significant association between baseline obesity and subsequent GHQ caseness emerged when GHQ caseness was assessed 10, 15, or 20 years after baseline (odds ratios between 1.35 and 1.48), and these associations remained unchanged when adjusted for baseline GHQ caseness. The stronger association with longer follow-up times most likely represented the effects of attrition because no such pattern was observed when the associations were examined in participants with full data over the follow-up period.

7.6. Associations between baseline GHQ caseness at phase 1 and obesity at phases 1 to 9

Purpose: The aim and structure of the current section is the same as in the previous section, except that here baseline GHQ caseness at phase 1 is used to predict obesity at phases 1 to 9.

Methods: Following the methods used in the previous section, cross-sectional and longitudinal associations are assessed with 5 separate linear regression models for each of the study phases. The longitudinal models are examined with and without adjustment for baseline obesity.

Results: Baseline GHQ caseness was not associated with obesity in cross-sectional or longitudinal models whether or not they were adjusted for baseline obesity status, or whether examining the association in the total sample or only in those with full data at all study phases (**Table 6-1**).

Comment: The present section suggests that GHQ caseness is not related to later obesity risk whether obesity is assessed 5, 10, 15, or 20 years later and whether or not baseline obesity is adjusted for.

Table 6-1. Separate logistic regression models for associations of baseline (phase 1) GHQ caseness with obesity in phases 1 to 9.

Outcome	Model 1: Unadjusted for baseline obesity	Model 2: Adjusted for baseline obesity	Model 3: Model 1 fitted in participants with full data	p for difference between Models 1 and 3	n
Obesity in					
Phase 1	1.10 (0.93, 1.31)	-	1.14 (0.82, 1.58)	0.758	10165
Phase 3	0.98 (0.82, 1.16)	0.95 (0.75, 1.19)	1.00 (0.77, 1.30)	0.842	7823
Phase 5	1.07 (0.90, 1.27)	1.06 (0.87, 1.30)	1.12 (0.91, 1.37)	0.456	5404
Phase 7	1.13 (0.98, 1.30)	1.16 (0.99, 1.36)	1.18 (0.98, 1.42)	0.450	6240
Phase 9	1.07 (0.93, 1.23)	1.08 (0.93, 1.27)	1.12 (0.93, 1.35)	0.363	5999

All models are adjusted for sex, age, and attrition indicator.

Models 1 are fitted in samples with maximum number of participants (numbers in the far right-hand column)

Models 2 are models 1, adjusted for baseline obesity

Models 3 are fitted in participants with full data available at each phase (n=3906)

7.7. Cross-sectional and longitudinal associations between obesity and GHQ caseness

Purpose: The section continues the analyses in the two previous sections in examining whether obesity and GHQ caseness are related to each other, and whether obesity predicts future risk of GHQ caseness or whether GHQ caseness predicts later obesity risk in longitudinal models spanning 5 to 20 years of follow-up. While the analysis in the two previous sections was based on separate ordinary linear regression models, the present section applied multilevel modeling to pool the longitudinal data from multiple study phases together in unified models with repeated measurements from the same individuals.

Methods: Multilevel logistic regression was used to predict the the risk of GHQ caseness by obesity, and vice versa, in cross-sectional and longitudinal analysis. To examine whether the longitudinal associations were dependent on the length of follow-up time, models with 5-, 10-, 15-, and 20-year follow-ups were fitted. Each participant could contribute a maximum of 4 person-observations to the 5-year analysis (data cycles consisting of phases 1 to 3; 3 to 5; 5 to 7; 7 to 9), 3 person-observations to the 10-year analysis (1 to 5; 3 to 7; 5 to 9), 2 person-observations to the 15-year analysis (1 to 7; 3 to 9), and 1 person-observation to the 20-year analysis (1 to 9). In addition to models unadjusted for outcome variable at data cycle baseline, baseline-adjusted models were fitted to provide a stronger setting for the assessment of temporal order between obesity and GHQ caseness.

Results: The associations of obesity with GHQ caseness assessed concurrently with obesity and longitudinally after 5, 10, 15, and 20 years of follow-up after obesity, are shown in **Table 7-1**. In cross-sectional analysis, the magnitude of the association between obesity and GHQ caseness was OR=1.27. As in the regression models fitted separately by study

phase in section 7.5, the longitudinal association between obesity and GHQ caseness increased in strength with longer follow-up from OR=1.16 over a 5-year interval to OR=1.63 over a 20-year interval. The odds ratios remained essentially the same when adjusted for obesity at baseline of the data cycle (**Table 7-1, Model 2**).

Table 7-1. Cross-sectional and longitudinal associations of obesity with GHQ caseness assessed with different time intervals.

Outcome: GHQ caseness assessed	Model 1: Unadjusted for baseline obesity OR (95% CI)	Model 2: Adjusted for baseline obesity OR (95% CI)	Model 3: Full data (n=3906) OR (95% CI)	n
Concurrently	1.27 (1.14, 1.42)	-	1.17 (1.00, 1.37)	35878 (10264)
5 years later	1.16 (1.00, 1.34)	1.14 (1.02, 1.28)	1.20 (0.99, 1.45)	25167 (8553)
10 years later	1.24 (1.02, 1.50)	1.21 (1.03, 1.44)	1.15 (0.90, 1.48)	17703 (7522)
15 years later	1.58 (1.23, 2.03)	1.53 (1.22, 1.93)	1.29 (0.91, 1.84)	12585 (7135)
20 years later	1.63 (1.24, 2.16)	1.66 (1.24, 2.22)	1.31 (0.87, 1.98)	6499 (6499)

All models adjust for sex, birth year, age, and attrition indicator.

Table 7-2. Cross-sectional and longitudinal associations of GHQ caseness with obesity assessed with different time intervals.

Oucome: Obesity assessed	Model 1: Unadjusted for baseline GHQ caseness OR (95% CI)	Model 2: Adjusted for baseline GHQ caseness OR (95% CI)	Model 3: Full data (n=3906) OR (95% CI)	n
Concurrently	1.29 (1.09, 1.55)	-	1.11 (0.86, 1.43)	35878 (10264)
5 years later	1.00 (0.81, 1.24)	1.06 (0.93, 1.20)	0.97 (0.74, 1.27)	23614 (8439)
10 years later	1.25 (0.95, 1.64)	1.22 (1.01, 1.46)	1.33 (0.97, 1.82)	16001 (6950)
15 years later	1.27 (0.88, 1.82)	1.20 (0.93, 1.55)	1.32 (0.83, 2.08)	12000 (6787)
20 years later	1.06 (0.91, 1.22)	1.11 (0.89, 1.38)	1.12 (0.93, 1.36)	6109 (6109)

All models adjust for sex, age, and attrition indicator. Birth year was not included in any of the models, because some of the models did not reach convergence when birth year was included together with time-varying age.

In the analysis of GHQ caseness and later obesity risk, some of the models failed to converge when birth year was included together with age as a time-varying factor in the model. In the interest of consistency, all the models presented in Table 7-2 are therefore fitted without birth year as a covariate. In addition to the cross-sectional association, only the baseline-adjusted association over a 10-year follow-up was statistically significant (OR=1.22). Although the unadjusted associations over 10-year and 15-year intervals were equal In terms of effect magnitude they were not statistically significant.

Comment: The multilevel regression models provide support for the longitudinal ordinary logistic regression models presented in sections 7.5. and 7.6. fitted separately for outcomes measured at different phases. Obesity was associated with future GHQ caseness more strongly the longer the time interval between measurement of obesity and subsequent GHQ caseness. GHQ caseness was not consistently associated with future obesity, although there were some suggestive associations over 10- and 15-years of follow-up. Hence, these results suggest that the temporal order between the two variables is from obesity to GHQ caseness but not the reverse. Unlike in the regression models presented previously, using only cross-sectional data from phase 1 (**Table 5-1** and **Table 6-1**), the multilevel logistic regression models indicated a significant cross-sectional association when the 5 study phases were pooled together (OR=1.27).

7.8. Change versus change analysis of BMI and GHQ

Purpose: While it is informative to examine cross-sectional and longitudinal associations between BMI and CMDs measured at different points in time, in terms of prevention and clinical practice a crucial question is whether (un)favourable change in either body weight or mental health is likely to result in (un)favourable change in the other. The present section takes advantage of the repeated measurements of BMI and GHQ to create change scores for the two variables to examine how within-individual changes in BMI are related to changes in GHQ, and vice versa. This analysis of change versus change is performed using time-lagged and concurrent time intervals in the exposure and outcome. In addition to assessing change as a linear exposure, non-linear models are fitted to assess whether an increase in the exposure is differently related to future change in the outcome than a decrease in the exposure. The models are also fitted separately by BMI category (normal weight, overweight, obese) and GHQ caseness (GHQ case versus non-case).

Methods: Change scores for BMI and continuous GHQ scores are created by subtracting the value of the variable at the previous study phase from the value of the variable at the current study phase. The associations between concurrent changes in BMI and GHQ are tested with these change score variables, i.e., how BMI change over 5 years is correlated with GHQ change over the same 5-year period. This analysis, however, cannot determine whether change in BMI precedes change in GHQ, or the reverse. To determine temporal order of the change scores, change in the exposure variable over 5 years is used to predict change in the outcome over the following 5 years, e.g., change in BMI between phases 3 and 5 is used to predict change in GHQ scores over phases 5 and 7.

For the non-linear modeling of the effects of increase vs. decrease in exposure, the method described by Naumova et al. [351] is used. A dichotomous variable indicating the direction of change is first created (0=change < 0; 1=change ≥ 0), and the change score and an interaction effect between the change score and the dichotomous indicator (but not the main effect of the dichotomous indicator) is included in the regression model. This allows the regression slope for the exposure variable to differ for increasing vs. decreasing values. The interaction term between the change score and the dichotomous indicator determines whether the regression slope is significantly different for a decrease compared to an increase in the exposure.

Results: In the analysis of concurrent changes, an increase in BMI correlated with a decrease in GHQ (**Table 8-1, Model 1**) and an increase in GHQ score correlated with a decrease in BMI (**Table 8-2, Model 1**).

Table 8-1. Change score analysis of BMI and GHQ with linear exposure variable.

	Model 1. Concurrent change scores			Model 2. Lagged change scores		
	B	95% CI	n	B	95% CI	n
A. BMI change predicting GHQ change (per 1 BMI unit)	-0.17	(-0.26, -0.09)	23076 (8315)	0.07	(-0.04, 0.19)	13630 (5322)
B. BMI change (per 1 BMI unit) predicting GHQ change in						
Normal weight	-0.43	(-0.58, -0.28)	11582 (5257)	0.10	(-0.10, 0.29)	7388 (3454)
Overweight	-0.09	(-0.22, 0.05)	8974 (4542)	0.13	(-0.05, 0.30)	5072 (2785)
Obese	0.02	(-0.15, 0.19)	2520 (1384)	-0.03	(-0.28, 0.22)	1170 (697)

Multilevel linear regression models, adjusted for age, sex, birth year and attrition indicator (n=8315 participants, 23076 person-observations). n=Number of person-observations (and persons)

Table 8-2. Change score analysis of GHQ and BMI with linear exposure variable.

	Model 1. Concurrent change scores			Model 2. Lagged change scores		
	B	95% CI	n	B	95% CI	n
A. GHQ change predicting BMI change (per 10 GHQ points)	-0.04	(-0.06, -0.02)	23076 (8315)	0.04	(0.01, 0.07)	13630 (5322)
B. GHQ change (per 10 GHQ points) predicting BMI change in						
Non-GHQ cases	0.02	(-0.01, 0.05)	17745 (7461)	0.06	(0.02, 0.09)	10432 (4834)
GHQ cases	-0.05	(-0.08, -0.01)	5331 (3477)	0.05	(0.01, 0.10)	3198 (2186)

Multilevel linear regression models, adjusted for age, sex, birth year and attrition indicator (n=8315 participants, 23076 person-observations). n=Number of person-observations (and persons)

These correlations were observed in normal weights but not in overweight or obese participants (**Table 8-1**), and in GHQ cases but not in GHQ non-cases (**Table 8-2**). In other words, decreasing BMI over time correlated with increasing GHQ scores over the same time period among normal-weight participants but not in overweights or obese participants. Similarly, increasing GHQ over time correlated with decreasing BMI over the same time period among participants with high GHQ scores (GHQ cases) but not in those with low GHQ scores (GHQ non-cases).

The analysis of change versus change with the change in the exposure and change in the outcome measured over different time periods produced quite different results. Change in BMI over 5 years did not predict future change in GHQ scores (**Table 8-1, Model 2**). This lack of association was observed in all weight groups. By contrast, increasing GHQ over a 5-year time period predicted increasing BMI 5 years later, which was observed in GHQ cases and non-cases (**Table 8-2, Model 2**).

Thus, the time-lagged association for GHQ caseness predicting BMI change was in the opposite direction than in the analysis of concurrent change.

Table 8-3. Change score analysis of BMI and GHQ with non-linearly modeled exposure variable.

	Decrease		Increase		p for difference	Total n
	B	95% CI	B	95% CI		
BMI change predicting future GHQ change (per 1 BMI unit)	0.33	(0.05, 0.61)	-0.04	(-0.20, 0.12)	0.05	13630 (5322)
BMI change (per 1 BMI unit) predicting future GHQ change in						
Normal weight	0.53	(-0.03, 1.10)	-0.04	(-0.29, 0.21)	0.11	7388 (3454)
Overweight	0.31	(-0.13, 0.75)	0.05	(-0.20, 0.30)	0.38	5072 (2785)
Obese	0.23	(-0.26, 0.73)	-0.24	(-0.64, 0.18)	0.23	1170 (697)

Multilevel linear regression models, adjusted for age, sex, birth year and attrition indicator.
n=Number of person-observations (and persons)

Table 8-4. Change score analysis of GHQ and BMI with non-linearly modeled exposure variable.

	Decrease		Increase		p for difference	Total n
	B	95% CI	B	95% CI		
GHQ change predicting future BMI change (per 10 GHQ units)	-0.02	(-0.06, 0.02)	0.10	(0.06, 0.15)	0.001	13630 (5322)
GHQ change (per 10 GHQ units) predicting future BMI change in						
Non-GHQ cases	-0.07	(-0.16, 0.03)	0.10	(0.05, 0.15)	0.006	10432 (4834)
GHQ cases	0.01	(-0.06, 0.07)	0.14	(0.03, 0.25)	0.08	3198 (2186)

Multilevel linear regression models, adjusted for age, sex, birth year and attrition pattern.
n=Number of person-observations (and persons)

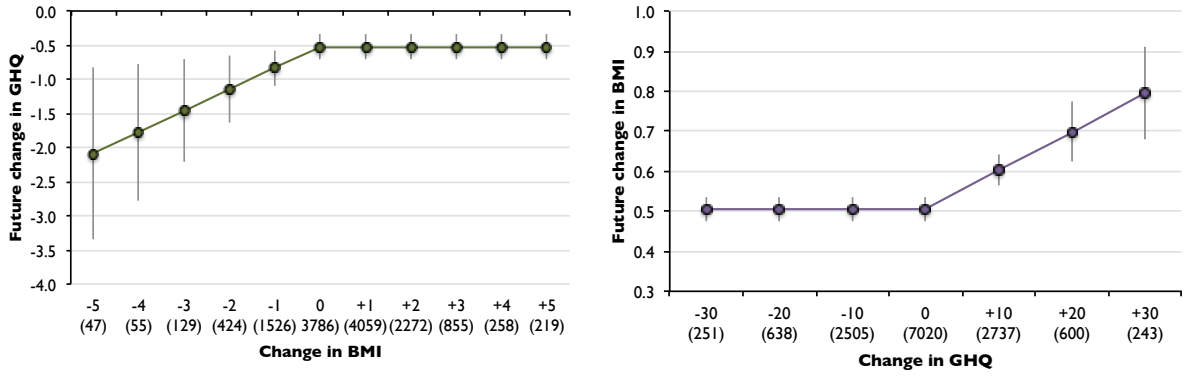


Figure 8-1. Non-linear change versus change analysis of BMI and GHQ. Left-hand panel shows that decreasing BMI predicted decreasing GHQ scores in the future, while increasing BMI was not associated with future change in GHQ. Right-hand panel shows that decreasing GHQ did not predict future change in BMI whereas increasing GHQ was associated with greater weight gain in the future. Error bars are 95% confidence intervals. See **Table 8-3** and **Table 8-4** for statistical details.

Next the possibility of non-linear change was introduced. As shown in **Table 8-3**, decreasing BMI predicted future decrease in GHQ (weight loss improves GHQ scores) while increase in BMI was unrelated with future GHQ change (weight gain does not affect GHQ scores). The association of decreasing BMI with decreasing GHQ scores was slightly stronger in normal weight participants than in the overweight and obese, but the confidence intervals for all the groups were too wide to make definite conclusions. The corresponding analysis for the other direction of temporality presented in **Table 8-4** shows that an increase in GHQ predicted a later increase in BMI (worsening GHQ scores lead to weight gain) but that a decrease in GHQ was unrelated to future BMI change (improving GHQ scores do not affect weight change). This association was similar in GHQ cases and non-cases. These non-linear associations for increase vs. decrease in the exposure associated with future change in the outcome are illustrated in **Figure 8-1** which plots the predicted change in the outcome as a function of the preceding change in the exposure.

Comment: Within-individual analysis of change provides more detailed information on the potential mechanisms connecting BMI and GHQ. The findings suggest that weight loss leads to future improvements in mental health, and worsening mental health tends to increase the risk of accelerated future weight gain. By contrast, long-term weight gain neither leads to worsening mental health, on average, nor does improving mental health protect against future weight gain. Thus, the temporal associations between BMI and GHQ may be bidirectional, but the nature of these associations may be quite different in terms of the mechanisms responsible for bringing about the associations.

7.9. Associations between obesity and GHQ caseness with the exposure assessed using a cumulative score

Purpose: As described in section 7.4., the risk of obesity increased progressively with the number of times the person had been obese in the preceding study phases, and a similar cumulative effect was observed for the risk of GHQ caseness. In this section, the cumulative score for obesity is used to predict future GHQ, and vice versa, to examine whether cumulative effects of obesity and GHQ caseness have different effects compared to obesity and GHQ caseness measured only based on one time point, as in section 7.7.

Methods: Cumulative exposure scores are calculated as described in section 7.4., i.e., by summing the number of times the person has been obese or a GHQ case in the previous study phases. Data were pooled over all study phases, and multilevel regression was used to estimate the associations.

Results: GHQ scores as a function of the number of times the person has been obese in the preceding study phases are shown in the left-hand panel of **Figure 9-1**. There was no significant linear trend between cumulative obesity score and GHQ ($p=0.64$), even though there was some indication of an inverse association in individuals who had been obese at three or four of the previous study phases. By contrast, the more times a participant had been a GHQ case at previous measurement phases, the higher the participant's BMI, as illustrated in right-hand panel of **Figure 9-1**. To test the robustness of the association, the multilevel models were fitted with within-individual (or 'fixed effect') estimator which estimates the association using only within-individual variation, in this case the same individuals having different values for the cumulative GHQ score and future BMI. The association was

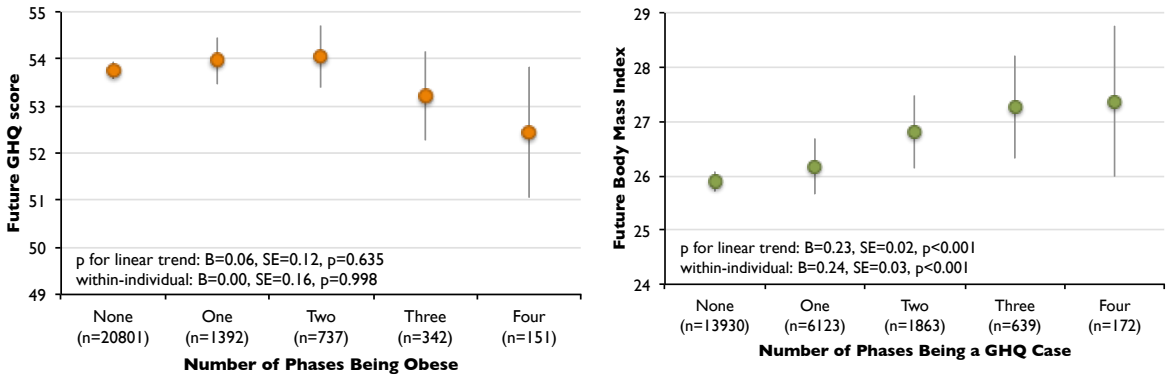


Figure 9-1. Associations between a cumulative score for obesity and future GHQ score (left-hand panel), and cumulative GHQ score and future BMI (right-hand panel). Predicted values from multilevel linear regression models, adjusted for age, sex, and attrition indicator. Error bars are 95% confidence intervals.

similar in the within-individual analysis and in the overall analysis, suggesting that the association was not caused by between-individual confounding factors.

Comment: The analysis of bidirectional associations between obesity and GHQ caseness in sections 7.6. and 7.7 suggested that obesity predicts GHQ caseness but not vice versa. The findings of the current section indicate that GHQ caseness may be relevant for increasing BMI only when the individual has an elevated GHQ score over longer periods of time, which is why study designs assessing GHQ as an exposure only at one point in time do not observe an association with BMI. Obesity did not have a cumulative effect on GHQ risk.

7.10. Mediator variables in the associations between obesity and GHQ caseness

Purpose: To examine whether the associations between obesity and GHQ caseness, and between BMI change and GHQ change, are explained by occupational grade, sleep duration, bodily pain, dietary patterns, longstanding illnesses, physical activity, smoking, or alcohol consumption.

Methods: The statistically significant associations between obesity and GHQ caseness reported in section 7.7 and between changes in BMI and GHQ reported in section 7.8 are refitted with adjustments for the covariates. In cross-sectional analyses, covariates are naturally assessed at the same study phase as the exposure and the outcome. In longitudinal analysis with follow-up interval spanning two consecutive study phases, data for covariates can be derived from the data cycle baseline or from the follow-up 5 years later when the outcome of interest is assessed. Here both methods were applied to test whether the measurement phase of the covariate affects the adjustment effect. In analyses of change in exposure versus change in outcome, the associations were adjusted for 1) covariate assessed at data cycle baseline and 2) change in the covariate over the same period of time as the change in the exposure. For models including non-linear change in the exposure (see section 7.8), the covariate was also modeled as non-linear using the same method used for the modeling of the exposure, as described in section 7.8 above.

Results: Cross-sectional and bidirectional longitudinal associations between obesity or GHQ caseness and the covariates are reported in **Table 10-1** and **Table 10-2**. When assessed concurrently (**Models 1**), obesity and GHQ caseness were associated with shorter sleep duration, higher bodily pain, lower physical activity, smoking, and higher risk of long

Table 10-1. Cross-sectional and longitudinal associations between obesity and study covariates. Multilevel linear and logistic regression models.

Covariate	Model 1: Cross-sectional B or OR (95% CI)	Model 2: Longitudinal, obesity predicting covariate B or OR (95% CI)	Model 3: Longitudinal, covariate predicting obesity OR (95% CI)
Continuous outcome (B coefficient, 95% CI)			
Occupational grade	-0.03 (-0.05, 0.00)	-0.03 (-0.06, 0.01)	0.83 (0.77, 0.91)
Sleep duration	-0.09 (-0.12, -0.07)	-0.07 (-0.11, -0.03)	0.82 (0.73, 0.92)
Bodily pain	0.30 (0.25, 0.35)	0.30 (0.24, 0.37)	1.16 (1.05, 1.28)
AHEI diet score	-1.57 (-2.11, -1.03)	-0.96 (-1.83, -0.09)	0.98 (0.97, 0.99)
Physical activity	-0.14 (-0.19, -0.10)	-0.14 (-0.20, -0.08)	0.89 (0.81, 0.97)
Dichotomous outcome (Odds ratios, 95% CI)			
Longstanding illness (0=no, 1=yes)	1.64 (1.48, 1.82)	1.37 (1.23, 1.53)	1.46 (1.20, 1.76)
Alcohol consumption (0=none/ moderate, 1=heavy)	1.11 (0.91, 1.35)	1.00 (0.77, 1.32)	1.18 (0.91, 1.53)
Smoking (0=no, 1=yes)	0.45 (0.35, 0.59)	0.91 (0.67, 1.24)	0.83 (0.58, 1.17)

Values are odds ratios of separate multilevel logistic regression models, adjusted for age at baseline, age at assessment, sex, birth year and attrition indicator.

standing illness. Obesity also correlated with a poorer diet score. Except for smoking, all of these associations for obesity were also significant when obesity was used to predict the covariates longitudinally over 5-year intervals (**Models 2**) or when the covariates were used to predict future obesity after 5 years of follow-up (**Models 3**). Again, except for smoking, the longitudinal associations in both directions for GHQ and the covariates replicated the cross-sectional results (**Table 10-2**).

The adjusted cross-sectional associations between obesity and GHQ caseness are shown in **Table 10-3**. Given that some of the study covariates were not assessed at all the study phases (see **Table 1-1**) and different covariates had varying numbers of missing values across the study phases, the first column of **Table 10-3** first shows the unadjusted association between obesity and GHQ caseness in the subsample with data on the covariate in question

Table 10-2. Cross-sectional and longitudinal associations between GHQ caseness and study covariates. Multilevel linear and logistic regression models.

Covariate	Model 1: Cross-sectional B or OR (95% CI)	Model 2: Longitudinal, obesity predicting covariate B or OR (95% CI)	Model 3: Longitudinal, covariate predicting obesity OR (95% CI)
Continuous outcome (B coefficient, 95% CI)			
Occupational grade	0.00 (-0.02, 0.01)	0.03 (0.01, 0.05)	0.97 (0.94, 1.00)
Sleep duration	-0.23 (-0.25, -0.21)	-0.06 (-0.08, -0.03)	0.86 (0.81, 0.90)
Bodily pain	0.57 (0.54, 0.61)	0.26 (0.22, 0.31)	1.41 (1.35, 1.46)
AHEI diet score	-0.30 (-0.67, 0.08)	0.18 (-0.37, 0.73)	1.00 (0.99, 1.00)
Physical activity	-0.14 (-0.17, -0.12)	-0.04 (-0.08, 0.00)	0.93 (0.89, 0.97)
Dichotomous outcome (Odds ratios, 95% CI)			
Longstanding illness (0=no, 1=yes)	1.68 (1.56, 1.81)	1.39 (1.29, 1.50)	1.51 (1.38, 1.65)
Alcohol consumption (0=none/ moderate, 1=heavy)	1.09 (0.96, 1.24)	1.03 (0.88, 1.21)	1.04 (0.93, 1.17)
Smoking (0=no, 1=yes)	1.25 (1.06, 1.47)	1.13 (0.93, 1.37)	1.08 (0.95, 1.24)

Values are odds ratios of separate multilevel logistic regression models, adjusted for age at baseline, age at assessment, sex, and attrition indicator.

(number of participants and person-observations reported in the right-most column of **Table 10-3**). This method of assessing the effects of adjustment for the covariates is used throughout the section from **Table 10-4** to **Table 10-7**. The second column of **Table 10-3** shows the cross-sectional association adjusted for each covariate. Adjusting for bodily pain attenuated the odds ratios from OR=1.31 to OR=1.10 (67% attenuation). Adjusting for sleep duration produced an attenuation from OR=1.27 to OR=1.21 (21% attenuation) and longstanding illness from OR=1.27 to OR=1.22 (17% attenuation). Other covariates had little if any effect on the cross-sectional association.

Table 10-4 reports the effects of covariate adjustment in the longitudinal analysis of obesity and GHQ caseness assessed over 5-year intervals (see section 7.7). Again, adjusting for bodily pain had the strongest attenuating effect (from OR=1.23 to OR=1.12 when adjusted for bodily pain at data cycle baseline; 48% attenuation), especially when bodily pain was

Table 10-3. Cross-sectional association between obesity and GHQ caseness, adjusted for covariates. Multilevel logistic regression models.

	Model 1: Base model	Model 2: Adjusted for covariate	
Covariate	OR (95% CI)	OR (95% CI)	n (participants, person-observations)
Occupational grade	1.27 (1.14, 1.42)	1.27 (1.14, 1.42)	10264 (35878)
Sleep duration	1.27 (1.14, 1.42)	1.21 (1.08, 1.35)	10259 (35772)
Bodily pain	1.31 (1.16, 1.49)	1.10 (0.97, 1.24)	8598 (25650)
AHEI diet score	1.32 (1.13, 1.53)	1.31 (1.13, 1.52)	8372 (17810)
Longstanding illness	1.27 (1.14, 1.42)	1.22 (1.09, 1.36)	10264 (35878)
Physical activity	1.26 (1.11, 1.42)	1.23 (1.08, 1.39)	10114 (29227)
Alcohol consumption	1.26 (1.11, 1.42)	1.26 (1.11, 1.42)	10235 (29607)
Smoking	1.29 (1.15, 1.44)	1.28 (1.15, 1.43)	10236 (35174)

Models adjusted for age at baseline, age at assessment, sex, and attrition indicator (Models 1) and additionally for a covariate (Model 2).

The unadjusted models are shown separately for each covariate because the number of participants varies depending on covariate.

Table 10-4. Longitudinal association between obesity and GHQ caseness, adjusted for covariates. Multilevel logistic regression models.

	Model 1: Base model	Model 2: Adjusted for covariate at baseline	Model 3: Adjusted for covariate at follow-up
Covariate	OR (95% CI)	OR (95% CI)	OR (95% CI)
Occupational grade	1.16 (1.00, 1.34)	1.15 (1.00, 1.33)	1.15 (1.00, 1.33)
Sleep duration	1.15 (0.99, 1.33)	1.13 (0.98, 1.30)	1.10 (0.95, 1.27)
Bodily pain	1.23 (1.04, 1.46)	1.12 (0.96, 1.32)	0.97 (0.82, 1.15)
AHEI diet score	1.12 (0.87, 1.44)	1.12 (0.87, 1.45)	1.11 (0.86, 1.44)
Longstanding illness	1.16 (1.00, 1.34)	1.13 (0.98, 1.30)	1.11 (0.96, 1.28)
Physical activity	1.20 (1.00, 1.43)	1.19 (0.99, 1.42)	1.16 (0.97, 1.40)
Alcohol consumption	1.18 (0.99, 1.40)	1.18 (1.00, 1.40)	1.18 (0.99, 1.40)
Smoking	1.17 (1.01, 1.35)	1.16 (1.00, 1.35)	1.16 (1.00, 1.34)

Models adjusted for age at baseline, age at assessment, sex, and attrition indicator (Models 1) and additionally for a covariate (Model 2). Base models are shown separately for each covariate because the number of participants varies between 5055 and 8553 participants (8488 to 25167 person-observations) depending on covariate.

Table 10-5. Associations between concurrent changes in BMI and GHQ score, adjusted for covariates. Multilevel linear regression models.

	Model 1: Base model	Model 2: Adjusted for covariate at data cycle baseline	Model 3: Adjusted for change in covariate
Covariate	B (95% CI)	B (95% CI)	B (95% CI)
Occupational grade	-0.17 (-0.26, -0.09)	-0.17 (-0.26, -0.09)	-0.17 (-0.26, -0.09)
Sleep duration	-0.16 (-0.25, -0.08)	-0.16 (-0.24, -0.07)	-0.18 (-0.26, -0.09)
Bodily pain	-0.15 (-0.25, -0.05)	-0.14 (-0.25, -0.04)	-0.17 (-0.27, -0.07)
AHEI diet score	-0.15 (-0.30, 0.00)	-0.15 (-0.30, 0.00)	-0.15 (-0.30, 0.00)
Longstanding illness	-0.17 (-0.26, -0.09)	-0.17 (-0.26, -0.08)	-0.17 (-0.26, -0.09)
Physical activity	-0.24 (-0.34, -0.14)	-0.24 (-0.35, -0.14)	-0.26 (-0.36, -0.16)
Alcohol consumption	-0.23 (-0.33, -0.12)	-0.23 (-0.33, -0.12)	-0.23 (-0.33, -0.12)
Smoking	-0.14 (-0.23, -0.05)	-0.14 (-0.23, -0.05)	-0.14 (-0.23, -0.05)

All models adjusted for age at baseline, age at assessment, sex, and attrition indicator

The unadjusted models are shown separately for each covariate because the number of participants varies between 4387 and 8315 participants (7806 to 23076 person-observations) depending on covariate (see **Table 1-1**).

Table 10-6. Association of decreasing BMI with future decrease in GHQ score, adjusted for covariates. Multilevel linear regression models.

	Model 1: Base model	Model 2: Adjusted for covariate at data cycle baseline	Model 3: Adjusted for non-linear change in covariate
Covariate	B (95% CI)	B (95% CI)	B (95% CI)
Occupational grade	0.33 (0.05, 0.61)	0.35 (0.07, 0.63)	0.33 (0.05, 0.61)
Sleep duration	0.34 (0.06, 0.62)	0.33 (0.04, 0.61)	0.34 (0.05, 0.62)
Bodily pain	0.33 (-0.01, 0.67)	0.34 (0.01, 0.67)	0.33 (-0.01, 0.67)
AHEI diet score	0.33 (-0.03, 0.70)	0.36 (0.01, 0.71)	0.33 (-0.03, 0.70)
Longstanding illness	0.33 (0.05, 0.61)	0.34 (0.06, 0.62)	0.33 (0.05, 0.61)
Physical activity	0.33 (0.05, 0.61)	0.33 (0.05, 0.61)	0.33 (0.05, 0.61)
Alcohol consumption	0.31 (0.03, 0.59)	0.31 (0.03, 0.59)	0.31 (0.03, 0.59)
Smoking	0.26 (-0.03, 0.54)	0.32 (0.04, 0.60)	0.26 (-0.02, 0.55)

All models adjusted for age at baseline, age at assessment, sex, and attrition indicator

The unadjusted models are shown separately for each covariate because the number of participants varies depending on covariate.

Table 10-7. Association of increasing GHQ score with future increase in BMI, adjusted for covariates. Multilevel linear regression models.

	Model 1: Base model	Model 2: Adjusted for covariate at data cycle baseline	Model 3: Adjusted for non-linear change in covariate
Adjusted for	B (95% CI)	B (95% CI)	B (95% CI)
Occupational grade	0.10 (0.06, 0.15)	0.10 (0.06, 0.15)	0.10 (0.06, 0.15)
Sleep duration	0.10 (0.06, 0.15)	0.10 (0.06, 0.15)	0.11 (0.06, 0.15)
Bodily pain	0.13 (0.08, 0.19)	0.14 (0.08, 0.19)	0.12 (0.07, 0.18)
AHEI diet score	0.14 (0.08, 0.19)	0.14 (0.09, 0.20)	0.14 (0.08, 0.19)
Longstanding illness	0.10 (0.06, 0.15)	0.10 (0.06, 0.15)	0.10 (0.06, 0.15)
Physical activity	0.11 (0.07, 0.15)	0.11 (0.07, 0.16)	0.11 (0.07, 0.15)
Alcohol consumption	0.11 (0.07, 0.15)	0.11 (0.06, 0.15)	0.11 (0.07, 0.16)
Smoking	0.10 (0.06, 0.15)	0.10 (0.05, 0.14)	0.10 (0.06, 0.15)

All models adjusted for age at baseline, age at assessment, sex, and attrition indicator

The unadjusted models are shown separately for each covariate because the number of participants varies depending on covariate.

assessed at the follow-up (OR=0.97; 100% attenuation of the positive association). Adjusting for sleep duration and longstanding illness accounted for 33% and 31% of the association, respectively, when the covariates were assessed at follow-up at the time of GHQ assessment.

The results for covariate-adjusted models of change versus change analysis are shown in **Table 10-5** (concurrent changes), **Table 10-6** (decreasing BMI predicting future decrease in GHQ), and **Table 10-7** (increasing GHQ predicting future increase in BMI). In these models, adjusting for any of the covariates had no substantial effect on the associations between changes in BMI and GHQ, whether the covariate was assessed at data cycle baseline or modeled as a change score in the same way as the exposure variable of interest was modeled.

Comment: In cross-sectional and longitudinal analysis, bodily pain was the most prominent covariate to attenuate the association between obesity and GHQ caseness. In longitudinal analysis predicting GHQ 5 years after the assessment of obesity, bodily pain re-

ported at the same measurement phase as GHQ attenuated the association between obesity and GHQ completely, suggesting that obesity is related to increased risk of GHQ caseness because obesity increases bodily pain which, in turn, is associated with higher GHQ scores. Longstanding illnesses and sleep duration were the two other covariates that had an attenuating effect on the obesity-GHQ association, accounting for 17% to 33% of the association.

7.11. Moderator variables in the associations between obesity and GHQ

Purpose: This section examines whether the associations between BMI and GHQ are modified by sex, age, occupational grade, and time-period. As reviewed in the introduction, these variables have been suggested to be potential modifying factors in the association between obesity and GHQ, but the empirical evidence to date is limited.

Methods: To assess whether there are consistent moderator effects in the association between BMI and GHQ, all the different statistical models described in earlier sections are rerun including an interaction effect between exposure (obesity or GHQ caseness; change in BMI or change in GHQ) and the moderator variable (sex, age, occupational grade, and time-period). The statistical significance of these interactions is first determined, and then the statistically significant interaction effects are investigated in more detail by examining the association of obesity and GHQ caseness stratified by the moderating factor.

Results: P-values for the interaction effects for the four covariates in different cross-sectional and longitudinal models are reported in **Table 11-1**. None of the moderator variables had a consistent effect across different statistical models, but there were some individual interaction effects, as described below.

Sex: Although there was no sex difference in the cross-sectional association between obesity and GHQ caseness (p=0638), a significant interaction effect indicated that lagged obesity predicted future risk of GHQ caseness in men (OR=1.42, CI=1.17-1.72, p<0.001) but not in women (OR=0.93, CI=0.74-1.18, p=0.56). There was also a sex difference in the lagged GHQ change in predicting future change in BMI, so that a decrease in GHQ was not associated with future change in BMI in men (B=-0.04; CI=-0.08, 0.01, p=0.123) or in women

Table 11-1. P-values for interaction effects between the exposure and moderator variables in different statistical models.

	Sex	Age	Grade	Time period
Model 1. Cross-sectional association	0.638	0.032	0.651	0.024
Model 2. Lagged obesity predicting future GHQ caseness (5-year interval)	0.011	0.727	0.640	0.883
Model 3. Lagged GHQ caseness predicting future obesity (5-year interval)	0.475	0.004	0.317	0.022
Model 4. BMI change predicting concurrent change in GHQ	0.817	0.153	0.265	0.254
Model 5. Lagged BMI change predicting future change in GHQ				
Increase in BMI	0.372	0.306	0.508	0.449
Decrease in BMI	0.106	0.065	0.310	0.693
Model 6. Lagged GHQ change predicting future change in BMI				
Increase in GHQ	0.086	0.391	0.324	0.880
Decrease in GHQ	0.009	0.832	0.533	0.201

Details of the models are described in earlier sections of the results.

(B=0.02; CI=-0.08, 0.11; p=0.722) whereas an increase in GHQ was associated with future increase in BMI somewhat more strongly in men (B=0.11; CI=0.06-0.16; p<0.001) than in women (B=0.09; CI=-0.01, 0.18; p=0.069).

Age: Age interactions were observed in cross-sectional analysis, and when lagged GHQ caseness was used to predict future obesity risk. As illustrated in **Figure 11-1**, the association between GHQ caseness and obesity strengthened with age.

Occupational grade: There was no significant modifying effects for occupational grade for any of the associations between BMI and GHQ.

Time period. The interaction effects for time period were the same as for age, i.e., in cross-sectional analysis and in lagged GHQ caseness predicting future obesity risk. Given the similarity, it is possible that the interactions for age and time-period both reflect the

same underlying interaction effects as both are concerned with the passage of time. To test the relative strengths of the interactions when included in the same model, cross-sectional and lagged longitudinal models were rerun by including interaction effects for both age and time-period. In cross-sectional analysis neither interaction effects were significant in the single model (p=0.778 for age, p=0.286 for time-period), while in the lagged analysis the age interaction was marginally significant (p=0.09) and the time interaction was not (p=0.70).

Comment: Of the 32 tests of interaction effects between the covariates and the exposures in different models of BMI and GHQ, 6 were statistically significant. Based only on chance, one would expect to find 32*0.05=1.6 or 2 significant effects with statistical significance at the 5% level. The strongest evidence for a moderating effect was for age. The cross-sectional association nd the longitudinal association of GHQ caseness predicting obesity risk 5 years later increased in strength with age. Obesity was associated with future GHQ caseness risk in the longitudinal analysis in men but not in women, and a similar sex difference was observed for the change score analysis in which an increase in GHQ score predicted a later increase in BMI more strongly in men compared to women.

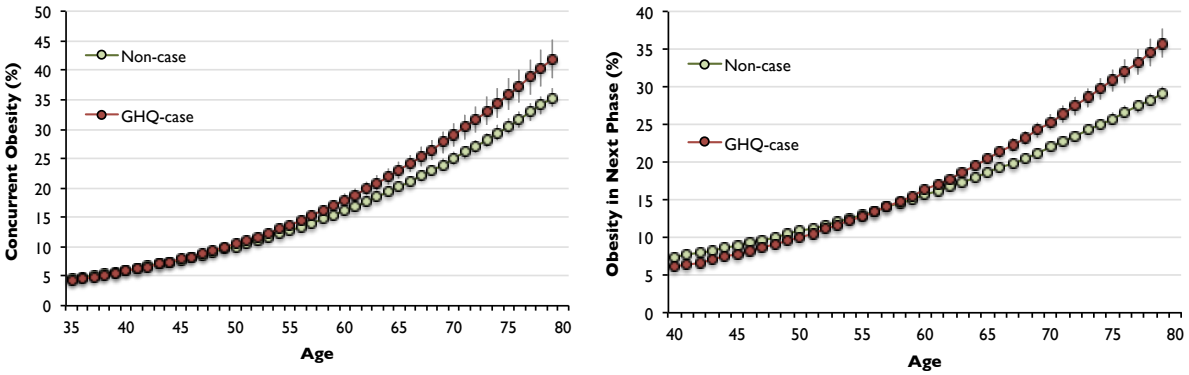


Figure 11-1. Interaction effects between GHQ caseness and age in predicting obesity in cross-sectional and longitudinal setting. Predicted values from interaction models presented in **Table 11-1**.

Chapter 8. Discussion

Research on the associations between excessive body weight and symptoms of depression, anxiety or other common mental disorders (CMDs) has produced rather mixed findings over the years. First, some of the early cross-sectional studies suggested that obesity may protect from the development of CMDs ([352,353]; see section 8.4. below), while several but not all subsequent cross-sectional studies provided evidence for a positive correlation between obesity and CMDs.[81,82] The more recent longitudinal studies have generally found support for a positive bidirectional association between obesity and CMDs, although many individual studies have observed no associations.[103] These inconsistencies have puzzled many scholars trying to integrate their own findings with the existing literature. Some researchers have argued that this line of research has been driven by the stubborness of the researchers rather than the robustness of the results. In discussing the absence of a substantial association between obesity and depression in their study of British adolescents, Wardle and colleagues[354] ponder

> "One interesting issue is why the belief that obese people, and especially obese children, are depressed, has not been rejected despite numerous studies producing negative findings. Perhaps it reflects sensitivity to and sympathy for the plight of obese people. Alternatively, it could be viewed as part of society's - and health professionals' - prejudice against obese people, involving the attribution of negative emotional characteristics along with the other negative stereotypes." (p. 641)

The present thesis was based on the assumption that the association between obesity and CMDs is unlikely to be spurious but that this association may be more specific or complex than postulated in simple cross-sectional and longitudinal studies. This may be the reason why the results from different studies with less sophisticated methodology have produced mixed findings, and why the nature of the bidirectional association has not been established with accuracy. As shown by the different statistical models applied in the present thesis, a single analysis method may not provide a full description because different mechanisms may be involved in different aspects of the association.

8.1. Synopsis of the main findings

First, obesity and CMDs followed different age trajectories. The proportion of obese participants increased throughout the age period from 35 to 79 years, whereas CMDs became less common especially between ages 50 and 65, after which there was no clear changes in CMDs with age. Second, the development of both obesity and CMDs was characterized by cumulative developmental patterns, that is, the risk of future obesity (or CMDs) increased progressively with the number of times the person had been obese (or had CMDs) in previous study phases. Third, standard longitudinal regression models suggested that obesity was prospectively associated with future CMDs, whereas CMDs did not predict future risk of obesity. Fourth, when cumulative exposure measures were used, chronic obesity over several study phases did not increase the risk of obesity any more than obesity in one study phase only. However, chronic CMDs exhibited a temporal dose-response association with the risk of obesity, so that only individuals with CMDs in several study phases over the follow-up phase had elevated risk of future obesity while no association was observed for short-term CMDs. Fifth, analysis of interrelated changes of BMI and CMDs indicated that weight loss

was associated with a future decrease in CMDs, and an increase of CMDs was associated with future increase in BMI. Weight gain, however, was not associated with future change in CMDs and improving levels of CMDs were not associated with a decrease in BMI. These results suggest that the associations between changes in BMI and CMDs are dependent on the direction of change in the exposure. Sixth, several potential mediators (SES, sleep duration, dietary patterns, physical activity, longstanding illness, alcohol consumption, smoking) had little if any explanatory power in accounting for the associations between BMI and CMDs. Bodily pain accounted for 67% of the cross-sectional and 48% of the longitudinal association between BMI and CMDs, but did not explain any of the associations of the interrelated changes between BMI and CMDs over time. Seventh, analysis of potential moderating factors (sex, age, SES, secular trends) provided little consistent evidence for these factors in modifying the associations between BMI and CMDs in different models. The most consistent evidence was observed for age, so that the cross-sectional association and the association between CMDs and the future risk of obesity increased in magnitude with age.

8.2. Strengths and limitations

8.2.1. Longitudinal data with multiple repeated measurements

The main strengths of the present study include a long follow-up period with repeated measurements of BMI and CMDs at 5 study phases, which made it possible to apply sophisticated and complex longitudinal models. A comparison between the conclusions drawn from the multiple repeat-measurement data and from the standard longitudinal method of measuring the exposure once at baseline and the outcome some years after, possibly adjusting for the level of outcome at baseline, suggested that multiple repeated measurements do

bring important additional information to our understanding of the longitudinal associations between obesity and CMDs. As reported in sections 7.5. and 7.6., standard analysis used in most previous studies of obesity and CMDs would have implied that obesity has a causal effect on risk of CMDs, or at least that obesity precedes CMDs not vice versa. The strengthening association between obesity and future GHQ caseness with a longer follow-up period might have led one to conclude that obesity has a cumulative effect on risk of CMDs. This turned out not to be the case as demonstrated by the analysis using cumulative scores presented in section 7.9.

Although the analyses covered several aspects of the association between obesity and CMDs, the longitudinal methods used in the present study were by no means exhaustive. In particular, latent trait models based on structural equation modeling (SEM) could have been added to further investigate longitudinal patterns, e.g., by examining measurement invariance of GHQ over time[355] or by modeling between-individual and within-individual associations separately by creating latent variables accounting for the stability in BMI and CMDs across the study phases and using residuals of these latent variable to indicate within-individual variance. Although multilevel models can be used to address most of the research questions that can be modeled using SEM, the use of latent variables could add additional information. However, these models were beyond the scope of the present thesis and will be explored in future research.

Another potential limitation regarding the present longitudinal data is that BMI and CMDs were measured at 5-year time intervals. Such intervals capture long-term developmental trends but may be too long to observe potential short-term effects of BMI and CMDs. For instance, rapid weight gain over one year may increase the risk of CMDs more strongly than equivalent weight gain over 5 years because the 1-year gain is more marked and may reflect different determinants than the 5-year weight gain. The analysis of bidirectional associations, cumulative effects and change vs. change should therefore be carried out with

datasets with annual or biannual measurements to evaluate whether similar or different patterns are observed with differing time intervals.

As discussed in section 7.2. on attrition patterns, the present data analysis strategy applied multilevel regression augmented with pattern mixture modeling to adjust for the data missingness related to selective attrition. These methods can produce valid estimates assuming that the attrition mechanisms are related only (or largely) to the covariates included in the models. The pattern mixture modeling method extends this by including a covariate of its own in the models to take into account differential attrition patterns between individuals. In the present analysis, adjusting for length of follow-up did not have substantial influence on the estimated developmental trajectories of obesity or CMDs (**Figure 3-3**), suggesting that selective attrition may not have been a major source of bias. However, no methods can definitively solve the problem of selective attrition, and it is not possible to know whether the potential bias would underestimate or overestimate the observed associations in the data. It would be useful to empirically assess the impact of selective attrition in epidemiological studies for example by comparing results from registry data (not affected by selective attrition) with parallel survey data (affected by selective attrition).

8.2.2. BMI as a measure of obesity

Assessment of BMI was based on objectively measured height and weight, so people's general tendency to slightly overestimate their height and underestimate their weight in self-reports did not confound the associations.[356-358] Body mass index is a reliable and valid indicator of the health risks associated with excess adiposity,[27,29,30,359] and it is the most commonly used method to assess obesity in epidemiologic studies. More accurate measures of body fat, such as bioelectrical impedance or hydro-densitometry, are often too expensive and impractical to use in large data collections, and other indicators of body fat, including skinfold thickness and waist circumference, are more difficult to measure accurately and

with consistency across large populations.[360] Although BMI may not always be an accurate measure of body fat at the individual level, it has proven to be one of the best proxy measures of body fat in studies examining associations of body fat at the population level.[360]

BMI has limitations in estimating body fat in persons who are very muscular or have lost muscle mass, and BMI does not capture any information of specific patterns of fat accumulation, such as abdominal adiposity.[360] In statistical terms, BMI may have high specificity but not so high sensitivity in correctly identifying obese individuals, as suggested by a study of 13,601 Americans comparing measures of BMI and body-fat percent determined by bioelectrical impedance.[361] Almost all (95% of men, 99% of women) participants categorized obese on the basis of BMI were also categorized obese based on body-fat percent (high specificity of BMI), but only 36% of men and 49% of women categorized obese by body-fat percent were categorized obese by high BMI (low sensitivity of BMI). The rather low sensitivity of BMI also resulted in underestimation of obesity prevalence based on BMI compared to body-fat percent (19% vs. 44% in men, 25% vs. 52% in women). It has also been suggested that not all health improvements associated with physical activity or other lifestyle changes, including reductions in visceral fat and cardiovascular risk factors, may be observed as weight loss based on measurement of BMI, suggesting that BMI may not be sensitive to all health changes related to obesity.[362]

Imprecisions related to BMI as a measure of adiposity may bias the results of studies using BMI if factors associated with measurement imprecision are systematically associated with covariates of interest. For instance, BMI may be a problematic measure of obesity in elderly people, who often lose height in old age. Such loss of height would tend to bias the measure of BMI upward.[363] The above-mentioned study comparing BMI and body-fat percent also observed that the diagnostic performance diminished with increasing age,[361] although other studies have suggested that BMI may still be a valid measure of obesity in the elderly on population level.[364] These potential problems imply that the present findings of

interaction effects between age and CMDs in predicting obesity need to be interpreted with caution, as BMI may not be an equivalent measure of adiposity across the adult life course.

8.2.3. GHQ caseness as a measure of CMDs

The GHQ is a well-validated instrument for screening CMDs[58-60,325] and GHQ scores are strongly associated with diagnoses of depressive and anxiety disorders.[59,60,326,327] Previous studies of obesity and different aspects of CMDs (depression, anxiety, psychosomatic complaints) have found no systematic evidence to suggest that obesity would be specifically associated with one aspect of CMDs but not with others[81,85,87] suggesting that a global assessment of CMDs is appropriate and no separation of different dimensions of CMDs is required.

The meta-analysis of longitudinal studies by Luppino et al.[103] suggested that obesity may be significantly (p=0.05) more strongly related to clinically diagnosed depression (OR=2.15, 1.48-3.12) than to self-reported symptoms of depression (OR=1.36, 1.03-1.80) and that clinically diagnosed depression predicts future obesity risk slightly but not significantly more strongly than self-reported depression symptoms (OR=1.71, 1.33-2.19 vs. 1.48, 1.17-1.87). These results from previous studies imply that the use of self-reported measures, such as the GHQ, may underestimate associations between obesity and psychiatric morbidity.

As in the case of BMI as a measure of body fat, it is not certain that GHQ is an equivalent measure of CMDs over the life course. Individual items of the GHQ may take on different meanings especially in older age. This could be studied in detail by examining age trajectories of individual GHQ items and by applying SEM models of measurement invariance[365,366] or alternative methods of examining stability and change in the psychometric structure of GHQ.

8.2.4. Study design

There are some limitations to the study sample and design that need to be considered when drawing conclusions on the associations between obesity and CMDs. First, being an occupational cohort, the Whitehall II sample is not completely representative of the general population. Occupational groups are, on average, by their very nature healthier than the general population, for example due to exclusion from sampling frame of unemployed individuals and individuals not able to work due to mental or physical limitations. Furthermore, two thirds of the cohort are male white collar workers in the civil service, potentially reducing the generalisability of the observed associations because of the occupationally selective nature of the sample. The range of variation in CMDs and BMI might therefore be narrower in the Whitehall II cohort than in the British general population. Range restriction of variable distributions often attenuates associations between two variables of interest.[367] The selective nature of the Whitehall II sample might therefore have attenuated the present estimates compared to what would have been observed in the general population. The restricted range of some variables may have masked associations or interactions that might exist in the general population. For example, the moderating effect of SES in the association between obesity and CMDs reported in some studies[87,266] would have been more difficult to observe in the Whitehall II sample even if it were present in the general population. On the other hand, the homogeneous nature of the Whitehall II sample may reduce the effects of confounding factors related to SES differences in the general populations because the participants are more similar to each other than people in the general population on average.

Second, the participants were aged between 35 and 55 at baseline, so no data on childhood or adolescent BMI or CMDs were available. As reviewed in Chapters 2 and 3, some evidence suggests that the association between obesity and CMDs may be particularly strong in adolescence,[151] and that adolescence may be a particularly important developmental period during which the association between depressive symptoms and later weight gain

trajectories originate.[95] Many psychiatric disorders have an early onset in adolescence and young adulthood,[51,52] and individual differences in body weight become more stabilized with age.[317] Thus, some of the more dynamic patterns might be observed only in younger ages. Given that our longitudinal data were derived only from adulthood, the present analyses could not address the hypothesis of childhood, adolescence or young adulthood being critical developmental periods for the origins of links between body weight and CMDs. It is important to apply the present analysis methods in younger samples to examine whether the developmental pattern are similar or different, and whether measurements at younger ages provide important additional insights into the bidirectional association between body weight and CMDs.

8.2.5. Measurement of covariates

Most of the covariates included in the study did not moderate or mediate the associations between obesity and CMDs. This is in contrast to some previous findings on potential moderators reviewed in Chapter 4, and to hypotheses proposed to explain the association between obesity and CMDs.[86,184,274,275] The lack of support for these hypothesis in the present study need to be interpreted within the limitations set by the measurement of the mediator and moderator variables. All the covariates were based on self-reported data, which introduces measurement error particularly in behavioral factors such as physical activity, alcohol consumption and dietary patterns that are often difficult for individuals to report accurately. Measurement error, in turn, reduces the possibility to observe statistically significant mediator or moderator effects. It is thus possible that some of the true mediator or moderator effects were not observed in the present analyses because of imprecise measurement of the covariates. However, one can argue that if some of the covariates had a major role in mediating the associations of obesity or CMDs, adjusting for imprecisely assessed but relevant covariates should have some influence on the examined associations. As most of the adjust-

ments had no discernible effect, it is unlikely that the present analysis would have missed the true mediator or moderator effects with substantial effect sizes.

Another methodological problem related to the use of self-reported data on CMDs and the covariates is the possibility of common informant bias. For example, the association between obesity and CMDs was substantially attenuated when adjusted for self-reported bodily pain, suggesting a potential mediator effect. However, the psychological content of self-reported CMD symptoms and experiences of bodily pain are likely to overlap substantially as somatic symptoms correlate with symptoms of anxiety and depression. This makes it difficult to interpret the "mediating" effect of bodily pain, because adjusting the association between obesity and CMDs for bodily pain may lead to overadjustment due to the overlap of self-reported CMDs and pain, almost as if one were to adjust the association between obesity and GHQ for another measure of CMDs. The use of more objectively measured indicators of pain or limitations of physical functioning (e.g., grip strength, walking speed, more specifically determined pain symptoms) could be used to further investigate the mediating role of bodily pain in explaining the association between obesity and CMDs.

8.3. Evaluating evidence from alternative models

A crucial issue in evaluating the association between obesity and CMDs is whether these two characteristics are causally related in a unidirectional or bidirectional manner, or whether the association between the two is caused by chance, confounding due to other unmeasured variables, or biases inherent in the study design. The starting premise of the present thesis was that any one methodologial approach to the study of the association between obesity and CMDs may not give the full and accurate picture of the true association. A given method may have a systematic bias for or against one interpretation, or produce chance findings not reflecting the true association. This is why it is important to try to triangulate the association between obesity and CMDs with alternative statistical models.

As reviewed in Chapters 3 and 4, previous studies on the bidirectional association between obesity and CMDs have not produced consistent findings. One way to try to solve this problem is to pool all available studies in a meta-analysis and to draw conclusions from the overall effects.[103] However, inconsistent findings may also imply that the association of interest is not due to a singular effect or mechanism. The overall association may reflect a combination of multiple mechanisms and processes that contribute to a different degree to different aspects of the bidirectional associations. Therefore, inconsistent results from different analyses need not imply contradictory findings. Different methods may address different aspects of the association in terms of, say, length of exposure or the mechanisms that account for differences between individuals vs. differences within the same individual over time. The evidence from alternative modeling approaches is next discussed with this point in mind.

8.3.1. Standard longitudinal models

As reviewed in the introduction, the meta-analysis of Luppino et al.[103] concluded that the association between obesity and depression is likely to be bidirectional, with the risk of depression being elevated by 55% in obese persons compared to normal-weight persons and the risk of obesity being elevated by 58% in depressed compared to non-depressed individuals. While this meta-analysis, based on 15 different studies, yields strong evidence of a bidirectional association, the findings may be confounded by study differences in the measurement of obesity (self-reported vs. objectively measured), measurement scales and assessment method for depression, time of follow-up, sample composition, and other potential factors that may bias the estimates upwards or downwards. Therefore, it is important to assess both directions of temporality in the same sample with the same measures.

Standard longitudinal methods used to evaluate the temporal direction of the association between obesity and CMDs have been the most commonly used methods in previous

longitudinal studies of obesity and CMDs. Using these methods, as in sections 7.5., 7.6. and 7.7., obesity was associated with an increased risk of CMDs assessed 5 to 20 years after the assessment of obesity, after adjustment for baseline CMDs (**Table 7-1**). By contrast, there was no significant association between CMDs and future risk of obesity (**Table 7-2**), except for one apparently spurious significant association between CMDs and obesity assessed 10 years later. The assumption that this finding is spurious is based on the fact that there were no consistent associations with other measurement intervals. These results suggest that any causal association between obesity and CMDs would run from obesity to increased risk of CMDs rather than the reverse.

Only a few other studies have assessed both temporal directions in the same study. The present results from time-lagged models are in agreement with at least two of them. In the Alameda County Study,[89,90] obesity was prospectively associated with an increased risk of depression over a 5-year follow-up (OR=1.79, CI=1.04-2.87) while depression at baseline was not associated with obesity 5 years later after obesity status at baseline had been adjusted for (OR=1.32, CI=0.65-2.69). This would seem to imply that obesity is a cause of depression but not the reverse. In the Maastricht Aging Study,[102] overweight at baseline predicted higher depressive symptoms 6 years later but baseline depressive symptoms were again unrelated to future risk of overweight. By contrast, a Finnish study of the metabolic syndrome and depression[101] reported that obesity at baseline was not significantly related to depressive symptoms over a 7-year follow-up period (OR=0.77, CI=0.38-1.56) but baseline depressive symptoms predicted increased risk of obesity at the end of the follow-up (OR=1.47, CI=0.80-2.71).

Taken together the results from these studies examining both temporal directions within a single analytic setting would seem to suggest that the association between obesity and CMDs is unidirectional such that obesity increases the risk of CMDs but not vice versa. However, data from other studies support the finding from the Finnish study, that is, CMDs

are also risk factors for obesity and weight gain.[151]. Adding weight to findings in the present study, similar evidence was obtained in more advanced longitudinal models in which the exposure was modeled with cumulative scores and changes over time, as described in the following section.

8.3.2. Cumulative effects of the exposure

For the determination of any potential dose-response relationship, the dose was conceptualized in terms of the persistence or cumulative effects of the exposure (obesity or CMDs) over time. Rather than measure the exposure only at one point in time, a cumulative score was created indicating the persistence of risk over the 5 to 20 years of follow-up. Assuming that there is a causal association, one would expect longer exposure to obesity and CMDs to predict CMDs and obesity, respectively, more strongly than a transient exposure.

Results from the cumulative analyses led to quite different conclusions as compared with those obtained from the time-lagged longitudinal models described above. The number of times a person had reported symptoms of CMDs at the data collection phases over the 5 to 20 -year follow-up period was linearly associated with future BMI (**Figure 9-1**), suggesting a dose-response relationship between persistent CMDs and BMI. By contrast, there was no increase in risk of CMDs associated with an accumulation of exposure to obesity; in fact, the dose-response curve in **Figure 9-1** suggests a slightly declining risk of CMDs associated with persistent obesity (obese at 3 or 4 study phases) compared to more transient exposure to obesity (obese at 1 or 2 study phases). This would imply that chronically obese individuals might adjust psychologically and socially to their excess body weight over time, thereby attenuating the negative mental health effects associated with obesity. However, the inverse association between persistent obesity and CMDs was not statistically significant, so no substantial conclusions should yet be drawn from these data alone.

The fact that a longitudinal, prospective association between CMDs and BMI was observed only with persistent, but not with transient, exposure to CMDs suggests that the process by which CMDs increase BMI may work over long periods of time. Compared to transient and short-lived exposure to CMDs, chronic exposure to CMDs may have different biological, psychological and social consequences related to body weight accumulation. This finding is in agreement with the study of Richardson et al.[139,140] in which the risk of adult obesity in women increased linearly with the number of times the participants had been depressed at 4 assessment times in adolescence. However, the present findings did not follow the same pattern as the findings of Mustillo and colleagues[99] which indicated that chronic childhood and adolescent obesity was associated with increased risk of depression in boys whereas no association was observed with obesity in childhood or adolescence alone.

Biologically, depression is known to be associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, e.g., with chronically elevated cortisol levels, which is a central neuroendocrine pathway underlying the psychophysiology of stress.[186-189] Repeated and chronic activation of the HPA axis and the secretion of cortisol, in turn, are involved with increased rate of fat accumulation and the risk of obesity.[170,179-183,368] Thus, psychosocial stress discussed in section 3.2 as a potential mechanism mediating the effect of CMDs on obesity risk might be a particularly relevant mechanism in the case of chronic CMDs. Psychological and social effects of persistent exposure to CMDs might lead to more marked declines in healthy behaviors, self-efficacy or social support, or other related mechanisms discussed in section 3.2, although there appear to be no empirical studies directly addressing this issue. The present findings provided little if any support for the relevance of health behaviours in mediating the association between CMDs and obesity.

To extend the analysis of cumulative effects further, two lines of research should be pursued. First, the present analysis did not examine how cumulative CMDs over time are associated with other outcomes besides BMI. Such analysis could provide additional clues to

the mechanisms accounting for the observed effects of persistent CMDs. Second, assuming that other determinants of weight gain have similar cumulative effects that are observed only when the covariate is measured repeatedly over time, future studies of BMI trajectories and obesity should analyze these other determinants using cumulative scores that take into account the persistent vs. non-persistent nature of the exposure. This may add to our understanding of the role of other determinants of weight gain besides CMDs.

The absence of a cumulative effect of obesity on CMDs, on the other hand, implies that the adverse mental health effects associated with obesity are more likely to act over a short rather than long term period. Psychological and social factors, such as negative self-image, stigma and discrimination related to obesity,[113,115] as well as some physical consequences, such as bodily pain and physical limitations caused by obesity,[109,250,369] could be expected to have such short-term and reversible effects; an obese person who loses weight to become normal-weight does not experience the physical limitations of obesity anymore, although some of the adverse effects of obesity, such as strain and damage caused to knee joints, would not be expected to be completely reversible especially at older ages, and these effects could have cumulative effects on CMDs.

Perhaps the lack of cumulative effects of obesity on CMDs reflects people's general propensity to adapt over time to circumstances, both negative and positive, that initially affect their mental wellbeing.[370-374] Although there are some notable exceptions to this rule,[375-379] the impact of many personal experiences and environmental changes on mental wellbeing seems to dilute over time, often within a couple of years, suggesting that individuals have a relatively stable "set point" of mental wellbeing around which life events introduce transient fluctuations in mental health.[371,373,374] Such a process of mental adaptation might explain the observed tendency for persistent obesity to be associated with slightly, albeit not significantly, lower levels of CMDs compared to non-persistent obesity (**Figure 9-1**). People who have

been obese over long periods of time may have become adjusted to their body weight, which is why persistent obesity is not associated with heightned risk of CMDs.

The lack of a cumulative effect of obesity is surprising considering that the standard time-lagged longitudinal models indicated that the association between obesity and future CMDs was stronger over longer compared to shorter follow-up intervals (OR=1.14, CI=1.02-1.28, over 5-year follow-up; OR=1.66, 1.24-2.22 over 20-year follow-up; **Table 7-1**). A cumulative effect of obesity could have explained this somewhat paradoxical pattern of results because obesity is highly stable over time, and therefore a long follow-up period in obese participants would indicate a high probability of persistent obesity, which would have explained the strengthening association with longer follow-up time. But this was not what the results of persistent obesity demonstrated. A more plausible explanation for the strengthening association is confounding effects due to attrition over the study period, because no changes in the odds ratios were observed with lengthening follow-up times when only participants with full data at all study phases were included (**Model 3, Table 5-1**).

8.3.3. Direction-specific change scores

Modeling of changes in BMI and CMDs rather than levels of BMI and CMDs in single points in time revealed new features of the association. An analysis of change in exposure versus change in outcome allows two important questions regarding causality to be addressed. First, if change in the exposure can be shown to precede change in the outcome, evidence for a causal association is strengthened. Second, whether or not the association between the outcome and exposure is reversible is crucial to inform public health interventions; it is important to know whether or not changing the level of the exposure variable would result in a change in the level of the outcome. In the present context, a reversible bidirectional association between obesity and CMDs would indicate that a successful attempt to decrease the prevalence of obesity would also result in an average improvement of mental

health in the population, and that a successful attempt to improve mental health would lead to a better weight control (overall decrease in the average BMI) in the population.

Naturally, the question of reversibility can be addressed with confidence only by randomized controlled trials (experimental studies) in which the researcher is able to modify the exposure independently of the participants' other characteristics that might influence the association of interest. As reviewed briefly in Chapter 5, studies of bariatric surgery and related treatment methods of obesity have suggested a beneficial effect of weight loss on mental health,[293-300] and that studies of depression treatment have reported both increases and decreases of body weight over the course of depression treatment.[230,276,301-304] Although these treatment studies, the studies of bariatric surgery in particular, might be considered as evidence for reversibility of the influence of obesity on CMDs, it is not clear how the results are generalizable to populations beyond the morbidly obese patients seeking bariatric surgery for their problems with obesity. Due to the lack of randomization in these studies, it is likely that the participants are not representative of obese individuals in general, most of whom do not seek drastic treatment options such as bariatric surgery, and the beneficial mental health effects of weight loss in this selected population may reflect their satisfaction with successful treatment rather than the association between obesity and mental health in general.

In the absence of randomized controlled trials to address the issue of reversibility, observational data can be used as an alternative approach to assess whether increases and decreases in the exposure are differently or similarly related to changes in the outcome. There appears to be no previous studies addressing this question in the association between obesity and CMDs. The present data did not provide support for a simple pattern of risk and reversibility. The modeling of time-lagged analysis of change in the exposure vs. change in the outcome indicated that an *increase* in CMDs over a 5-year period is associated with an *increase* in BMI in the 5-year period following the change in CMDs (**Figure 8-1**). No association between a decrease in CMDs and subsequent change in BMI were observed. By con-

trast, a *decrease* in BMI was associated with a subsequent *decrease* in CMDs whereas an increase in BMI was unrelated to future changes in CMDs. These observations would seem to suggest causal roles for a *decrease in BMI* and an *increase in CMDs*, implying that a bidirectional association between obesity and CMDs may not develop in a reciprocal manner. Rather, there appear to be non-reversible, ratchet-like effects which create a positive association between BMI and CMDs because 1) CMDs increase BMI and 2) weight loss improves mental health.

The association between an increase in CMDs and subsequent weight gain was moderate in magnitude. Compared to no change, a 10-point increase (about 1 standard deviation of change) in GHQ score increased the rate of future weight gain by one-fifth (0.50kg/m² vs. 0.60kg/m² per five years). A 2-unit decrease in BMI (slightly more than 1 standard deviation of change) more than doubled the rate of subsequent decrease in CMDs by (0.52 points vs. 1.15 points per five years). However, in absolute terms these differences are rather modest. Antidepressant treatment has been shown to improve mental health scores by 1.5 to 2 standard deviations when measured with the SF-36 mental health component score.[380-383] Thus, a depressed person quitting antidepressant treatment or a person otherwise experiencing an equivalent 2 standard deviation decline in their level of mental well-being would be expected to gain only an extra 0.20 BMI-units of weight over 5 years. Similarly, the 0.6-unit difference in GHQ scores associated with a 2-unit loss in BMI is only about 5% of the change observed for antidepressant treatment. Assuming that the effect sizes were similar in clinical interventions, the present findings would seem to suggest that CMDs are not crucial to weight management and weight loss is not an effective way to treat CMDs. However, randomized controlled trials should be carried out to directly test whether the effect sizes are comparable before the present results are applied in clinical settings.

How should we interpret these quite specific findings from the analysis of change in the exposure vs. change in the outcome? Weight gain and improving mental health are nor-

mative in middle age and early old age, as shown in section 7.3. It therefore appears that only changes deviating from these normative patterns are predictive of future changes in BMI and CMDs - a decrease in BMI predicting an improvement in mental health and a deterioration in mental health predicting an increase in BMI. Given public health messages on avoiding weight gain, intentional long-term weight loss in adulthood might improve mood (and alleviate symptoms of CMDs) by giving individuals a sense of self-efficacy, perhaps accompanied by other life-style modifications. Worsening mental health, on the other hand, may increase weight gain by leading to a diminished motivation for self-care, increase in unhealthy habits such as emotional overeating and reduced physical activity, or to neuroendocrinological changes in the HPA axis, which may induce weight gain.[170,179-183]

The analysis of change in the exposure versus change in the outcome paints quite a different picture of the bidirectional association between BMI and CMDs than the time-lagged longitudinal models discussed above. While the time-lagged longitudinal models showed a clear association between obesity and future CMDs, the analysis of change demonstrated no significant association between weight gain and subsequent increase in CMDs. This may be due to the differences in the questions the two methods address. Given the high stability of BMI over time, the time-lagged longitudinal models primarily address the issue of the between-individual association of obesity and CMDs, that is, whether obese persons have higher levels of CMDs than normal-weight persons. The analysis of change in the exposure vs. change in the outcome, in contrast, removes the between-individual variance from the analysis by concentrating only on within-individual changes, and therefore addresses the question of whether individuals who gain weight also experience increasing levels of CMDs. Hence, different results from these two analysis methods need not indicate contradictory or inconsistent findings, as they are concerned with different kinds of processes accounting for the association between body weight and CMDs.

Improving mental health associated with intentional and successful weight loss is plausible given the attempts by many people to lose weight. However, the absence of an association between weight gain and increasing CMDs, and the presence of an association between obesity and CMDs suggests that the latter association may not be causal in the way it is often interpreted to be. If obesity was causally related to CMDs because obesity brings with it various biological, psychological and social factors that adversely affect mental health, one would expect within-person weight gain to increase that person's level of CMD. The results could be more plausibly interpreted to suggest that obesity and CMDs are correlated with each other because of mechanisms that vary between individuals but not within individuals. As a hypothetical example, if the association between obesity and CMDs were due to common genetic effects,[384] one would expect to observe an association between obesity and CMDs when comparing different individuals with each other but not when comparing levels of BMI and CMDs within the same individuals over time, because the genetic background of those individuals would not change. Of course, the between-individual variance need not to be due to genetic effects specifically but could also reflect differences in other biological, psychological or social variables influencing both obesity and CMDs. For instance, various inflammatory markers (e.g., C-reactive protein and interleukin 6) have been suggested to account for the association between obesity and depression, as inflammation may be involved in both conditions.[385]

For the other direction of association - the influence of CMDs on obesity risk and weight gain - the results from the cumulative models and the analysis of change in the exposure versus change in the outcome were at least partly in agreement. The former indicated that persistent CMDs increase future BMI and the latter implied that an increase in CMDs over time predicts future increases in BMI within individuals, thus providing a more convincing causal interpretation for the association of CMDs and weight gain. However, the analysis of change in the exposure vs. change in the outcome did not support the reversibili-

ty of this association, as decreasing levels of CMDs over time were unrelated to future changes in BMI.

8.3.4. Mediating mechanisms

Some of the plausible mechanisms for each direction of causality between obesity and CMDs were introduced in sections 2.2. and 3.2. Obesity may increase the risk of CMDs via (1) limited physical functioning and bodily pain, (2) stigma and discrimination associated with obesity, (3) internalization of negative self-image and generalized perceptions of poor physical and mental health caused by obesity. CMDs may increase the risk of obesity via (1) psychosocial stress and associated physiological mechanisms involved in energy reservation, (2) dysfunctional health behaviours following depressed and anxious mood, (3) low self-efficacy in weight management and lack of social support from others, and (4) antidepressant use.[184,274,275,386]

While many alternative explanations have been put forward, these explanations have rarely been systematically explored in other studies besides the study initially suggesting the mechanism. In the present study, several covariates were adjusted for in order to test potential confounding and/or mediating mechanisms, as described in section 7.10. These covariates included occupational grade, sleep duration, bodily pain, dietary patterns, longstanding illnesses, physical activity, alcohol consumption, and smoking. Adjustment for bodily pain (self-reported by the participants using the 4-item "bodily pain" subscale of the SF-36 questionnaire) attenuated the cross-sectional association by two-thirds and the longitudinal association between obesity and CMDs by almost one-half. Other covariates had mostly minor or negligible effects on the associations between obesity (or change in BMI) and CMDs (or changes in CMDs).

Results from the mediation analyses thus partly supported the hypothesized pathway by which obesity increases levels of bodily pain which, in turn, is associated with an in-

creased risk of CMDs. Physical health is an important determinant of mental health, although subjectively reported physical health has been shown to correlate with mental health more strongly than objectively assessed physical health,[373] which probably reflects the heightened sensitivity to physical illnesses and symptoms in people suffering from mental health problems. This makes it somewhat difficult to interpret the attenuation due to bodily pain, as the reporting of bodily pain may be confounded by symptoms of CMDs. Nevertheless, bodily pain and limited physical functioning have been among the most prominent candidates suggested to explain the influence of obesity on CMDs, and the present mediation analysis provided empirical evidence only for this pathway and not for others.

In within-individual change analysis, adjustment for bodily pain or any other covariates had no discernible influence on the change versus change analysis of BMI and CMDs, irrespective of temporal direction or the method of adjustment (covariate reported at baseline data collection or assessed with change scores calculated over time concurrently with the change score in the exposure variable). It needs to be emphasized that the adjustment in the case of change in BMI predicting future change in CMDs was concerned with how weight loss preceded future decrease in CMDs rather than how weight gain would precede increase in CMDs. Thus, one would expect to observe a mediating effect of bodily pain in this analysis of change in the exposure vs. change in the outcome only if the effects of BMI and bodily pain were reversible, i.e., that weight loss would lead to decreasing bodily pain which would then lead to improving mental health.

8.3.5. Moderator effects

If the associations between obesity and CMDs were observed only in some sub-samples of the population, this might give clues to the mechanisms mediating the associations. Several candidates for modifying factors in the associations between obesity and CMDs have been proposed but the evidence for any of them has not been consistent.[87,184,274,275,387] As

reviewed in Chapter 4, the most prominent candidates have included age, sex, socioeconomic status, chronicity, and time-period effects.

In the present study, most robust evidence for a modifying effect was observed for age, which significanly modified the cross-sectional association and the longitudinal association of CMDs predicting future obesity risk (**Table 11-1**). In both instances, the association between obesity and CMDs became stronger with increasing age, suggesting that CMDs may be relevant for increasing the risk of obesity only after 60 years of age. No significant moderator effect was observed for age in longitudinal models of obesity predicting subsequent risk of CMDs. This pattern does not support either of the a priori hypotheses put forward in the introduction, one suggesting that the obesity would become a stronger predictor of CMDs with age due to the increasing prevalence of physical illnesses and limitations caused by obesity, and the other suggesting that obesity might become a weaker predictor of CMDs with age if the stigma and discrimination associated with obesity became less severe with age. Instead, the present findings suggest that the nature of CMDs in increasing obesity risk may be different for older compared to younger individuals. The explanation for this effect remains to be further examined.

It is often assumed that obesity and CMDs would be more strongly related in women than in men because physical appearance is believed to be more important for mental well-being of women. The present results do not support such a sex difference as the longitudinal association between obesity and subsequent CMDs was observed in men (OR=1.42, CI=1.17-1.72) but not in women (OR=0.93, CI=0.74-1.18). The Whitehall II sample is not a representative sample of men and women, as most of the civil servants (and thereby Whitehall II participants) are male, and women civil servants are unlikely to be representative of British women in general. The absence of a longitudinal association between obesity and CMDs might therefore reflect the selective nature of the women in the Whitehall II sample.

Previous studies have produced inconsistent findings concerning sex differences, and the overall evidence from the meta-analysis of Luppino et al.[103] suggested no sex differences in the association in either direction. Simon et al. suggested that differences in statistical power may be one of the methodological factors contributing to the sex differences observed in some of the studies as women tend to have higher levels of CMDs than men, thereby providing greater statistical power to detect associations in women. Simple stratification by sex may lead to spurious conclusions of sex differences. For example, in the NHANES III survey,[388] obesity was associated with depression in women (OR=1.82, CI=1.01-3.30) but not in men (OR=1.73, CI=0.56-5.37). This result is sometimes cited by other researchers as indicating a sex difference[83,386] even though the odds ratios were very similar in both sexes, albeit not significant in men. A statistical test would indicate a similar association in men and women.

Socioeconomic status (SES) and time period (secular trends in obesity and/or CMDs) might also modify the social circumstances in which obesity and CMDs influence each other. Both covariates are related to differences in the prevalence of obesity,[87] which could influence the social salience of obesity and therefore the negative mental health effects of obesity due to stigma and discrimination.[125,126,258,266] However, no evidence for interaction effects with SES was observed in the present study. Time period showed the same interaction effects with obesity as age, and additional analyses suggested that the interaction effects were mainly due to age rather than time period, although the issue could not be determined with certainty due to the close correlation between age and time period in the study.

Assuming that body dissatisfaction is more distressing for women and that women are judged more frequently on the basis of their physical appearance than men, the lack of a female-specific association between obesity and CMDs and the stronger association between CMDs and obesity in men would seem to suggest that factors related to social stigma and discrimination may not be the forces driving the potential causal association between obesi-

ty and CMDs. The absence of interaction effects with SES or time period, and the strengthening rather than weakening association with age, would also be somewhat surprising if social stigma, negative self-image or discrimination were responsible for the association between obesity and CMDs. It seems reasonable to hypothesize that an association between obesity and CMDs driven by social stigma, negative self-image or discrimination would have been modified by sex, age, SES and time period differently than was observed here. This evidence is only indirect and circumstantial, of course, and it does not provide a strong argument against the hypothesis that psychosocial pathways link obesity and CMDs. Direct measures of the relevant psychosocial factors were not available in the present study. However, the lack of support for these hypothesized moderator effects needs to be taken into account when considering the totality of evidence.

8.4. Additional evidence from Mendelian randomization studies

The present study was concerned with various longitudinal methods in examining the association between obesity and CMDs. Two recent studies have assessed the potential causal influence of obesity on CMDs by applying the method of Mendelian randomization, or instrumental variables (IV) regression with genetic instruments.[389-391] IV-regression is based on the idea of using an instrument to restrict the range of the exposure in predicting the outcome so as to reduce the influence of confounding in the association.[392-398] A valid instrument is a covariate that is associated with the exposure, and with the outcome only via its association with the exposure, but is not correlated with factors confounding the association between the exposure and outcome. The outcome of interest is then predicted only with the variance in the exposure that is associated with the unconfounded instrument, thus removing the effects of confounding factors. The method has been favored especially by

economists trying to estimate the true causal effects of various individual characteristics or policies.

Mendelian randomization is IV regression with measured genetic variants as the instruments.[394] Given that genotypes of individuals are determined by the random allocation of alleles from the parents in the formation of gametes and in conception, the genotypes are less likely to be biased by common confounds, such as socioeconomic factors and health behaviours.[398] Genetic variants underlying individual differences in BMI can therefore be used as instruments for BMI, that is, symptoms of CMDs are predicted with the genetic variance in BMI associated with the genetic instrument included in the study.

In the first Mendelian randomization study of BMI and CMDs carried out in the Whitehall II study, the *FTO* gene was used as an instrument for obesity and CMDs were assessed with the GHQ.[389] The positive association between obesity and CMDs observed with phenotypic data was also observed in the Mendelian randomization analysis, providing supporting evidence for a causal association between obesity and increased risk of CMDs. By contrast, a large Danish study of 53,221 participants[390] using the *FTO* and *MC4R* genes as instruments for BMI found a positive association between obesity and symptoms of CMDs in the phenotypic analysis (e.g., risk of reporting "feels like giving up" associated with obesity vs. normal weight: OR=1.33, CI=1.21-1.46), but a strong, albeit imprecisely estimated, negative association when applying Mendelian randomization (OR=0.25, CI=0.04-1.66).

Thus, the association of obesity with risk of CMDs appears inconsistent also in Mendelian randomization studies, even though the method has been suggested to improve data analysis based on observational data by removing common confounding influences. Mendelian randomization is not a method without limitations,[391,393] the most problematic assumption being that the genetic effects of specific 'obesity genotypes' on CMDs are mediated only via BMI. It is quite possible that the *FTO*, *MC4R*, and other genotypes influence CMDs via other pathways besides their associations with body weight (pleiotropic effects), in

which case they would not be valid instruments for obesity or BMI in Mendelian randomization studies. Unfortunately, there are no Mendelian randomization studies that have assessed the other direction of causality, that is, whether genetic instruments for CMDs are associated with BMI.

8.5. The competing "jolly-fat" hypothesis

In contrast to the overall evidence from studies to date[81,103] and most results of the present study, some studies have reported the diametrically opposite effect, that obesity has a protective effect against CMDs or depression. Indeed, one of the earlier articles of obesity and mental health in modern medical journals was entitled *"Jolly fat: relation between obesity and psychoneurosis in general population"*[352] which gave rise to the "jolly fat" -hypothesis of obesity. The paper, published in the British Medical Journal, showed that obese individuals had lower levels of anxiety (men and women) and depression (men only) than their normal weight counterparts. The finding was later replicated by the same research group in another sample.[353]

Some of the more recent studies have provided additional evidence for the jolly-fat hypothesis. In 2,245 men and women above age 50 living in California, USA, obese men had lower odds (OR=0.28) of being depressed, as indicated by high scores in the self-reported Beck's Depression Inventory.[399] Data from the US National Longitudinal Alcohol Epidemiologic Survey (NLAES) of 16,764 men and 23,322 women, obesity increased the risk of being depressed in women but decreased the risk of depression by 37% in men.[253] In the Renfrew/Paisley study of 7036 men and 8327 women living in the Scottish towns of Renfrew and Paisley, near to Glasgow, obese individuals were less likely (OR=0.52, 0.33-0.84) than normal-weight individuals to have a hospital admission due to depression.[400] And as described earlier, Gariepy et al.[97] showed an inverse association between obesity and incident depression in men (HR=0.71, 0.51-0.98).

In the present analysis of concurrently measured changes BMI and CMDs were inversely associated with each other, so that an increase in BMI over a 5-year period correlated with a decrease in levels of CMDs, which would be in agreement with the jolly fat -hypothesis. However, the association between a decrease in BMI and an increase in CMDs could also reflect some underlying disease or deteriorating general health, as many diseases and chronic medical illnesses are accompanied by weight loss. The onset of psychiatric disorders is also often associated with weight loss, which could account for the apparent association between lower weight and increased levels of CMDs. To date, plausible mechanisms explaining the inverse association between BMI and CMDs remain to be identified and demonstrated. Given the wealth of data and plausible mechanisms suggesting a positive association between obesity and CMDs, the evidence for a causal effect of obesity on lower rather than higher risk of CMDs remains relatively weak and without a convincing mechanism to explain the association.

Despite the inconsistent evidence supporting the jolly-fat hypothesis, a rather consistent protective role of obesity has been observed in studies of suicide. Several studies have reported that obese people are less likely to die by suicide than their leaner counterparts,[401-404] and obesity has also been associated with a lower probability of attempted (non-fatal) suicides.[405] However, a recent study found that obese individuals who had gone through bariatric surgery had an elevated risk of dying by suicide during the 10 years after the surgery,[406] although this finding may be unrelated to the mechanisms accounting for the inverse association between BMI and suicide risk observed in the general population.

The inverse association between obesity and suicide appears to be quite robust across studies, but the explanation for it is yet unclear. Mukamal and Miller[402] assessed whether obesity was associated with suicide risk factors, including alcohol use, mental health, marital status, firearm ownership, and risk-taking behaviours. All the conventional risk factors for suicide were inconsistently associated with BMI, indicating that they were

unlikely to mediate the observed relationship of BMI with lower risk of suicide. Others have suggested that the association may not be causal but rather reflect some unidentified confounding[405,407] or the influence of incident psychiatric disorder on weight loss and heightened suicide risk; unexplained weight loss seems to be more strongly related to suicide risk than BMI per se.[408] The possible protective association of obesity in relation to suicide and CMDs thus remains unexplained and poorly understood, and the status of the jolly-fat hypothesis is upheld only by occasional studies reporting an inverse association between obesity and symptoms of CMDs, and most of these studies have not pursued the topic beyond the demonstration of a simple inverse correlation. Alternative methods and more detailed analysis are needed to build a more coherent body of research investigating the circumstances in which obesity may protect from mental health problems.

8.6. Conclusions and future directions

8.6.1. Bidirectional association reconsidered

Previous results from standard longitudinal studies of obesity and CMDs have suggested that the association is bidirectional with almost equal effect magnitudes in both directions.[85,103,151] The present study demonstrates that such a conclusion is not completely warranted when evidence from different longitudinal analysis methods are considered together. Moreover, different patterns of association between obesity and CMDs are unlikely to reflect the same etiologic factors or causal mechanisms but rather multiple independent mechanisms. A similar conclusion was reached in the recent study of Gariepy et al.[97] in which obesity was positively associated with the prevalence of depression but inversely associated with depression incidence, implying that various alternative causal mechanisms may be at work.

Based on the present results, evidence for a causal influence of CMDs on weight gain and increased risk of obesity would seem to be fairly strong. This remains despite the lack of association between baseline CMDs and future obesity in standard longitudinal models; measurement of CMDs at one point in time may not be sufficient to detect the association, because persistent rather than transient exposure to CMDs is relevant for weight gain. This was shown in the analysis of cumulative CMDs which demonstrated a linear dose-response relationship between the number of times a participants reported CMDs and future BMI. An increase in CMDs over time also predicted subsequent increase in BMI over the following five years, providing further support for a causal association inferred by within-individual changes. These two findings suggest that CMDs are likely to have a causal effect on weight gain, especially when symptoms of CMDs are persistent, although the possibility of time-varying confounding factors cannot be ruled out. A decrease in CMDs was not associated with future weight loss, which implies a lack of reversibility. Perhaps improving mental health is not a strong enough factor to reverse existing adverse effects of CMDs on weight gain.

Obesity predicted higher levels of CMDs in longitudinal regression models, but there was no evidence for a dose-response relationship between weight gain and subsequent increase in CMDs in terms of within-individual changes. Thus, the association of obesity with CMDs appears to represent mainly a between-individual association in which within-individual weight gain does not affect changes in levels of CMDs. This between-individual association might be explained by biological comorbidity or other individual characteristics that act as common causes for the development of obesity and CMDs (see below). By contrast, weight loss was associated with subsequent decrease in CMDs, which may represent the positive experiences associated with successful long-term weight loss, possibly accompanied by other life-style modifications. The inverse association between concurrent weight loss

and increasing CMDs, on the other hand, may be due to medical or psychiatric illnesses that cause an increase in CMDs and cause weight loss.

Many of the explanations and interpretations offered above represent post hoc explanations that were developed after the empirical results had been observed. Although they are all possible and some maybe highly plausible, they should be interpreted cautiously before confirmation by additional independent studies. Unfortunately, the covariates included in the present study offered limited additional information concerning potential mechanisms.

8.6.2. Pathways of biological comorbidity

Considering the findings and limitations of the present study, one of the most promising avenues for future research on obesity and CMDs would probably be the investigation of their biological comorbidity.[185] This could be especially useful for elucidation of the cross-sectional association between obesity and CMDs that may be unrelated to mechanisms accounting for the dynamic within-individual changes in BMI and CMDs. The choice was made not to include any measures of biological markers, such as cholesterol, blood pressure or inflammation in the present study as the additional level of complexity was beyond the scope of this thesis. Several recent studies have suggested that obesity and mood disorders may share common pathophysiological pathways, including the HPA axis, immuno-inflammatory reactions and insulin signaling.[385,409-414] For example, obesity and mood disorder may both represent pro-inflammatory states, in which case their association might be explained by underlying inflammatory processes.[385] Biological markers could also help to explain some of the dynamic longitudinal associations between obesity and CMDs.

The inclusion of biological markers in future studies of obesity and CMDs is important because this may facilitate specification of the association with relevant biological pathways. For instance, if the inflammation hypothesis is correct, BMI and CMDs might be asso-

ciated with each other only to the extent they are associated with the inflammatory markers, while other sources of variance in BMI and CMDs would represent only noise that attenuates the true association due to inflammatory processes. There is also some inconsistent evidence suggesting a genetic link between obesity and CMDs.[384,415,416] One study reported that the association between obesity and chronic pain may also share familial background,[417] implying that adjusting for bodily pain in the association between obesity and CMDs may adjust for common genetic factors rather than for mediating pathways of the causal effects of obesity. These initial findings suggest that future studies need to consider biological and genetic effects together with phenotypic data to test alternative causal models explaining the association between obesity and CMDs.

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Appendix. STATA code for the analyses

```
sp       =   sex
age      =   continuous age
age_b    =   age at baseline
ob       =   dichotomous obesity
d_ghq    =   dichotomous GHQ
illf     =   longstanding illness
smoke    =   smoking
alc3     =   alcohol consumption
aika     =   year
bmi      =   continuous BMI
bg3      =   occupational grade
sleep    =   sleep duration
sf_bp    =   bodily pain
ahei     =   AHEI dietary patterns
pa4      =   physical activity
ghq10    =   GHQ score divided by 10
age5     =   continuous age divided by 5
pmix     =   pattern mixture variable of attrition (pmixr=reverse-coded pmix)
alcd     =   dichotomous alcohol consumption
bmir3    =   categorical BMI (normal weight, overweight, obese)

lag_*        =   variable value at the previous study phase
fwd_*        =   variable value at the next study phase
c_*          =   change score of the variable between the current and next phase
c_fwd_*      =   change score of the variable between the next phase and the phase after that
base_*       =   variable value at baseline
sel_crs      =   selection of cross-sectional sample
sel_lag      =   selection of the 2-phase time-lagged sample
sel_fwd      =   selection of the 3-phase time-lagged sample
full_data    =   indicator of full covariate data
cd_*         =   dichotomous indicator for the non-linear analysis of change
```

```
//  Table 1-1.
//  Descriptive statistics of the main sample
foreach catv in sp bg3 ob d_ghq illf smoke alc3 {
    tab `catv' aika if sel_crs<., col
    }
foreach des in sp age bmi c_bmi ghq c_ghq sleep sf_bp ahei pa4 {
    table aika if sel_crs<., c(mean `des' sd `des' n `des')
    }
```

```
//  Table 1-2.
//  Descriptive statistics of the sample by analysis design
global dedif sp age bmi ob ghq d_ghq bg3 lag_age sleep sf_bp ahei illf pa4
matrix d1=J(13, 9, .)
local irow 0
foreach des in $dedif {
    local ++irow
    xtsum `des' if sel_crs<.
    matrix d1[`irow',1]=r(mean)
    matrix d1[`irow',2]=r(sd)
    xtsum `des' if sel_lag<.
    matrix d1[`irow',3]=r(mean)
    matrix d1[`irow',4]=r(sd)
    xtsum `des' if sel_fwdchg<.
    matrix d1[`irow',5]=r(mean)
    matrix d1[`irow',6]=r(sd)
    }
    matrix colnames d1=m(crs) sd(crs) m(lag) sd(lag) m(fwd) sd(fwd)
    matrix rownames d1=$dedif
    matrix list d1, format(%9.2f)

    xtsum sp if sel_crs<.
    xtsum sp if sel_lag<.
    xtsum sp if sel_fwd<.

foreach catv in sp ob d_ghq illf smoke alc3 {
    xttab `catv' if sel_crs<.
    xttab `catv' if sel_lag<.
    xttab `catv' if sel_fwd<.
    }
//  Table 2-1.
//  Participation patterns with each row representing a specific
//  combination of participation and non-participation,
//  listed in order of descending frequency
xtdes if sel_crs<., patterns(31)
```

```
//  Table 2-2.
//  Baseline characteristics according to attrition pattern indicator
global fup age bmi ghq bg3 sleep sf_bp_imp1 ahei_imp1 pa4
matrix d2=J(8, 10, .)
local irow 0
foreach des in $fup {
    local ++irow
    summ `des' if pmix==4 & aika==1
    matrix d2[`irow',1]=r(mean)
    matrix d2[`irow',2]=r(sd)
    summ `des' if pmix==3 & aika==1
    matrix d2[`irow',3]=r(mean)
    matrix d2[`irow',4]=r(sd)
    summ `des' if pmix==2 & aika==1
    matrix d2[`irow',5]=r(mean)
    matrix d2[`irow',6]=r(sd)
    summ `des' if pmix==1 & aika==1
    matrix d2[`irow',7]=r(mean)
    matrix d2[`irow',8]=r(sd)
    summ `des' if pmix==0 & aika==1
    matrix d2[`irow',9]=r(mean)
    matrix d2[`irow',10]=r(sd)
    }
    matrix colnames d2=m(4) sd(4) m(3) sd(3) m(2) sd(2) m(1) sd(1) m(0) sd(0)
    matrix rownames d2=$fup
    matrix list d2, format(%9.2f)
tab pmix if aika==1
foreach catv in sp ob d_ghq illf smoke alc3 {
    tab `catv' pmixr if aika==1, col
    }
```

```
//  Table 2-3.
//  Predicting non-participation in the next study phase
//  by covariates in the preceding study phase (odds ratios).
global dcov sp age5 bmi ob ghq10 d_ghq bg3 sleep sf_bp_imp1 ahei_imp1 illf smoked pa4 alcd
local irow 0
matrix dop=J(14, 8, .)
foreach v of global dcov {
    local ++irow
    forvalues a=1(2)7 {
        local j=`a'+1
        logit dropout `v' sp age if aika==`a'
        matrix dop[`irow',`a']=exp(_b[`v'])
        matrix dop[`irow',`j']=(1-(normal((sqrt(_b[`v']^2))/_se[`v'])))*2
    }
}
matrix rownames dop=$dcov
matrix colnames dop=OR_1 p_1 OR_3 p_3 OR_5 p_5 OR_7 p_7
matrix list dop, format(%9.3f)
tab dropout aika if sel_crs<., col
```

```
//  Table 4-1.
//  Transition matrices of obesity status with different follow-up intervals.
tab fwd5_ob fwd0_ob, col
tab fwd10_ob fwd0_ob, col
tab fwd15_ob fwd0_ob, col
tab fwd20_ob fwd0_ob, col

//  Table 4-2.
//  Transition matrices of GHQ caseness with different follow-up intervals
tab fwd5_dghq fwd0_dghq, col
tab fwd10_dghq fwd0_dghq, col
tab fwd15_dghq fwd0_dghq, col
tab fwd20_dghq fwd0_dghq, col
```

```
//  Table 5-1.
//  Separate logistic regression models for associations of
//  baseline (phase 1) obesity with GHQ caseness in phases 1 to 9.
*model 1 & 3
forvalues i=1(2)9 {
quietly logistic d_ghq base_ob sp age if aika==`i' // & full_data<.
quietly estout, cells("b(fmt(%8.2f)) ci(par(( - )))") eform
quietly tempvar ma
quietly matrix `ma'=r(coefs)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "    " e(N)
    }
*p-values for differences between models 1 and 3
forvalues i=1(2)9 {
logistic d_ghq i.fdata##i.base_ob sp age if aika==`i'
}
*model 2
forvalues i=3(2)9 {
quietly logistic d_ghq base_ob base_dghq sp age if aika==`i' // & full_data<.
quietly estout, cells("b(fmt(%8.2f)) ci(par(( - )))") eform
quietly tempvar ma
quietly matrix `ma'=r(coefs)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "    " e(N)
    }
```

```
//  Table 6-1.
//  Separate logistic regression models for associations of
//  baseline (phase 1) GHQ caseness with obesity in phases 1 to 9.
* models 1 & 3
forvalues i=1(2)9 {
quietly logistic ob base_dghq sp age if aika==`i' & full_data<.
quietly estout, cells("b(fmt(%8.2f)) ci(par(( - )))") eform
quietly tempvar ma nu
quietly matrix `ma'=r(coefs)
quietly gen `nu'=e(N)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "  " `nu'
    }
* p-values for interactions
forvalues i=1(2)9 {
logistic ob i.fdata##i.base_dghq sp age if aika==`i'
}
forvalues i=3(2)9 {
quietly logistic ob base_dghq base_ob sp age if aika==`i'
quietly estout, cells("b(fmt(%8.2f)) ci(par(( - )))") eform
quietly tempvar ma nu
quietly matrix `ma'=r(coefs)
quietly gen `nu'=e(N)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "  " `nu'
    }
```

```
//  Table 7-1.
//  Cross-sectional and longitudinal associations of obesity with GHQ caseness
//  assessed with different time intervals
forvalues i=0(5)20 {
*   quietly xtlogit fwd`i'_dghq ob sp i.pmix age_b age if d_ghq<., or   // unadjusted
*   quietly xtlogit fwd`i'_dghq ob sp i.pmix age_b age d_ghq, or    // adjusted
    quietly xtlogit fwd`i'_dghq ob sp i.pmix age_b age if d_ghq<. & full_data<., or // full data
    quietly tempvar ma ng
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `ma'=r(coefs)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "   " %9.3f `ma'[1,4] "
" e(N) "   " `ng'
    }

* intraclass correlation
xtreg bmi
```

```
//  Table 7-2.
//  Cross-sectional and longitudinal associations of GHQ caseness with obesity
//  assessed with different time intervals
forvalues i=0(5)20 {
*   quietly xtlogit fwd`i'_ob d_ghq sp i.pmix age if ob<., or
*   quietly xtlogit fwd`i'_ob d_ghq sp i.pmix age ob, or
    quietly xtlogit fwd`i'_ob d_ghq sp i.pmix age if ob<. & full_data<., or
    quietly tempvar ma ng
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `ma'=r(coefs)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "   " %9.3f `ma'[1,4] "
" e(N) "   " `ng'
    }

* intraclass correlation
xtreg ghq
```

```
//  Table 8-1.
//  Change score analysis of BMI and GHQ with linear exposure variable
//  (n=8315 participants, 23076 person-observations)
* model 1, concurrent change
xtreg c_ghq i.pmix sp age_b age c_bmi if sel_chg<.
* by BMI category
forvalues i=1/3 {
    xtreg c_ghq i.pmix sp age_b age c_bmi if bmir3==`i' & sel_chg<.
    }

* model 2, lagged change
xtreg c_fwd_ghq i.pmix sp age_b age ghq c_bmi if sel_fwdchg<.
* by bmi groups
forvalues i=1/3 {
    xtreg c_fwd_ghq i.pmix sp age_b age ghq c_bmi if bmir3==`i' & sel_fwdchg<.
    }
```

```
//  Table 8-2.
//  Change score analysis of GHQ and BMI with linear exposure variable
//  (n=8315 participants, 23076 person-observations).
* model 1, concurrent change
xtreg c_bmi i.pmix sp aika age bmi c_ghq10 if sel_chg<.
*by ghq caseness
forvalues i=0/1 {
    xtreg c_bmi i.pmix sp age_b age bmi c_ghq10 if d_ghq==`i' & sel_chg<.
    }
* model 2, lagged change
xtreg c_fwd_bmi i.pmix sp age_b age bmi c_ghq10 if sel_fwdchg<.
*by ghq caseness
forvalues i=0/1 {
    xtreg c_fwd_bmi i.pmix sp aika age bmi c_ghq10 if d_ghq==`i' & sel_fwdchg<.
    }
```

```
//  Table 8-3.
//  Change score analysis of BMI and GHQ with non-linearly modeled exposure variable.
* main
xtreg c_fwd_ghq i.pmix sp age_b age ghq c_bmi b0.cd_bmi#c.c_bmi if sel_fwdchg<.
lincom c_bmi + 0.cd_bmi#c.c_bmi
lincom c_bmi + 1.cd_bmi#c.c_bmi
* by bmi category
forvalues i=1/3 {
   xtreg c_fwd_ghq i.pmix sp age_b age ghq c_bmi b0.cd_bmi#c.c_bmi if bmir3==`i' & sel_fwdchg<.
   lincom c_bmi + 0.cd_bmi#c.c_bmi
   lincom c_bmi + 1.cd_bmi#c.c_bmi
   }
```

```
//  Table 8-4.
//  Change score analysis of GHQ and BMI with non-linearly modeled exposure variable.
* main
xtreg c_fwd_bmi i.pmix sp age_b age bmi c_ghq10 b0.cd_ghq#c.c_ghq10 if sel_fwdchg<.
lincom c_ghq10 + 0.cd_ghq#c.c_ghq10
lincom c_ghq10 + 1.cd_ghq#c.c_ghq10
* by ghq caseness
forvalues i=0/1 {
    xtreg c_fwd_bmi i.pmix sp age_b age bmi c_ghq10 b0.cd_ghq#c.c_ghq10 if d_ghq==`i' &
sel_fwdchg<.
    lincom c_ghq10 + 0.cd_ghq#c.c_ghq10
    lincom c_ghq10 + 1.cd_ghq#c.c_ghq10
    }
```

```
//  Table 10-1.
//  Cross-sectional and longitudinal associations of obesity with study covariates

* continuous covariates
foreach med in grade sleep sf_bp ahei pa4 {
    quietly tempvar base ng
*   quietly xtreg `med' ob sp i.pmix age_b age if `med'<.           // model 1
*   quietly xtreg fwd_`med' ob sp i.pmix age_b age if `med'<.       // model 2
    quietly xtlogit fwd5_ob `med' sp i.pmix age_b age if `med'<., or        // model 3
    gen `ng'=e(N_g)
*   quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))")
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f
`base'[1,4] "    " e(N) "   " `ng'
    }

* dichotomous covariates
foreach med in illf alcd smoked {
    quietly tempvar base ng
*   quietly xtlogit `med' ob sp i.pmix age_b age if `med'<., or         // model 1
*   quietly xtlogit fwd_`med' ob sp i.pmix age_b age if `med'<., or     // model 2
    quietly xtlogit fwd5_ob `med' sp i.pmix age_b age if `med'<., or        // model 3
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f
`base'[1,4] "    " e(N) "   " `ng'
    }
```

```
//  Table 10-2.
//  Cross-sectional and longitudinal associations of GHQ caseness with study covariates

*continuous covariates
foreach med in grade sleep sf_bp ahei pa4 {
    quietly tempvar base ng
*   quietly xtreg `med' d_ghq sp i.pmix age_b age if `med'<.            // model 1
*   quietly xtreg fwd_`med' d_ghq sp i.pmix age_b age if `med'<.        // model 2
    quietly xtlogit fwd5_dghq `med' sp i.pmix age_b age if `med'<., or      // model 3
    gen `ng'=e(N_g)
*   quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))")
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f
`base'[1,4] "    " e(N) "   " `ng'
    }

*dichotomous covariates
foreach med in illf alcd smoked {
    quietly tempvar base ng
*   quietly xtlogit `med' d_ghq sp i.pmix age_b age if `med'<., or          // model 1
*   quietly xtlogit fwd_`med' d_ghq sp i.pmix age_b age if `med'<., or      // model 2
    quietly xtlogit fwd5_dghq `med' sp i.pmix age_b age if `med'<., or      // model 3
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f
`base'[1,4] "    " e(N) "   " `ng'
    }
```

```
//  Table 10-3.
//  Cross-sectional association between obesity and GHQ caseness, adjusted for covariates.

* model 1: unadjusted
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly tempvar base ng
    quietly xtlogit fwd0_dghq ob sp i.pmix age_b age if `med'<., or
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f
`base'[1,4] "    " e(N) "   " `ng'
    }
* model 2: adjusted
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly tempvar base ng
    quietly xtlogit fwd0_dghq ob `med' sp i.pmix age_b age if `med'<., or
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f
`base'[1,4] "    " e(N) "   " `ng'
    }
```

```
//  Table 10-4.
//  Longitudinal association of obesity with GHQ caseness, adjusted for covariates.

* model 1: unadjusted
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly tempvar base ng
    quietly xtlogit fwd5_dghq ob sp i.pmix age_b age if `med'<. & fwd_`med'<., or
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f `base'[1,4] "    " e(N) "   " `ng'
    }

* model 2: adjusted for data cycle baseline
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly tempvar base ng
    quietly xtlogit fwd5_dghq ob `med' sp i.pmix age_b age if `med'<. & fwd_`med'<., or
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f `base'[1,4] "    " e(N) "   " `ng'
    }

* model 3: adjusted for forward data cycle
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly tempvar base ng
    quietly xtlogit fwd5_dghq ob fwd_`med' sp i.pmix age_b age if `med'<. & fwd_`med'<., or
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))") eform
    quietly matrix `base'=r(coefs)
    di as result %9.2f `base'[1,1] " " %9.2f `base'[1,2] %9.2f `base'[1,3] "   " %9.3f `base'[1,4] "    " e(N) "   " `ng'
    }
```

```
//  Table 10-5.
//  Association between concurrent changes in BMI and GHQ score, adjusted for covariates.

* model 1: unadjusted
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly xtreg c_ghq c_bmi i.pmix sp age_b age if sel_chg<. & c_`med'<.
    quietly tempvar ma ng
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))")
    quietly matrix `ma'=r(coefs)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "   " %9.3f `ma'[1,4] "
" e(N) "   " `ng'
    }

* model 2: baseline adjusted
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly xtreg c_ghq c_bmi `med' i.pmix sp age_b age if sel_chg<. & c_`med'<.
    quietly tempvar ma ng
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))")
    quietly matrix `ma'=r(coefs)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "   " %9.3f `ma'[1,4] "
" e(N) "   " `ng'
    }

* model 3: adjusted for change in covariate
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly xtreg c_ghq c_bmi c_`med' i.pmix sp age_b age if sel_chg<. & c_`med'<.
    quietly tempvar ma ng
    gen `ng'=e(N_g)
    quietly estout, cells("b(fmt(%8.2f)) ci(par(( - ))) p(fmt(%8.3f))")
    quietly matrix `ma'=r(coefs)
    di as result %9.2f `ma'[1,1] " " %9.2f `ma'[1,2] %9.2f `ma'[1,3] "   " %9.3f `ma'[1,4] "
" e(N) "   " `ng'
    }
```

```
//  Table 10-6.
//  Association of decreasing BMI with future decrease in GHQ score, adjusted for covariates.

* model 1: unadjusted
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
    quietly xtreg c_fwd_ghq i.pmix sp age_b age ghq c_bmi b0.cd_bmi#c.c_bmi if sel_fwdchg<. &
c_`med'<.
    tempvar dec_b inc_b dec_lci inc_lci dec_hci inc_hci
    quietly lincom c_bmi + 0.cd_bmi#c.c_bmi
    gen `dec_b'=r(estimate)
    gen `dec_lci'=r(estimate)-(1.96*r(se))
    gen `dec_hci'=r(estimate)+(1.96*r(se))
    quietly lincom c_bmi + 1.cd_bmi#c.c_bmi
    gen `inc_b'=r(estimate)
    gen `inc_lci'=r(estimate)-(1.96*r(se))
    gen `inc_hci'=r(estimate)+(1.96*r(se))
    di as result %9.2f `dec_b' " " %9.2f `dec_lci' %9.2f `dec_hci' " " ///
    %9.2f `inc_b' " " %9.2f `inc_lci' %9.2f `inc_hci'
    }

* model 2: adjusted for non-linear covariate change
foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
*   quietly xtreg c_fwd_ghq i.pmix sp age_b age ghq c_bmi b0.cd_bmi#c.c_bmi c_`med'
b0.cd_`med'#c.c_`med' if sel_fwdchg<. & c_`med'<.
    quietly xtreg c_fwd_ghq i.pmix sp age_b age ghq c_bmi b0.cd_bmi#c.c_bmi `med' if
sel_fwdchg<. & `med'<.
    tempvar dec_b inc_b dec_lci inc_lci dec_hci inc_hci
    quietly lincom c_bmi + 0.cd_bmi#c.c_bmi
    gen `dec_b'=r(estimate)
    gen `dec_lci'=r(estimate)-(1.96*r(se))
    gen `dec_hci'=r(estimate)+(1.96*r(se))
    quietly lincom c_bmi + 1.cd_bmi#c.c_bmi
    gen `inc_b'=r(estimate)
    gen `inc_lci'=r(estimate)-(1.96*r(se))
    gen `inc_hci'=r(estimate)+(1.96*r(se))
    di as result %9.2f `dec_b' " " %9.2f `dec_lci' %9.2f `dec_hci' " " ///
    %9.2f `inc_b' " " %9.2f `inc_lci' %9.2f `inc_hci'
    }
```

```
652 //  Table 10-7.
653 //  Association of increasing GHQ score with future increase in BMI, adjusted for covariates.
654
655 * model 1: unadjusted
656 foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
657     quietly xtreg c_fwd_bmi i.pmix sp age_b age bmi c_ghq10 b0.cd_ghq#c.c_ghq10 if sel_fwdchg<.
    & c_`med'<.
658     tempvar dec_b inc_b dec_lci inc_lci dec_hci inc_hci
659     quietly lincom c_ghq10 + 0.cd_ghq#c.c_ghq10
660     gen `dec_b'=r(estimate)
661     gen `dec_lci'=r(estimate)-(1.96*r(se))
662     gen `dec_hci'=r(estimate)+(1.96*r(se))
663     quietly lincom c_ghq10 + 1.cd_ghq#c.c_ghq10
664     gen `inc_b'=r(estimate)
665     gen `inc_lci'=r(estimate)-(1.96*r(se))
666     gen `inc_hci'=r(estimate)+(1.96*r(se))
667     di as result %9.2f `dec_b' " " %9.2f `dec_lci' %9.2f `dec_hci' " " ///
668     %9.2f `inc_b' " " %9.2f `inc_lci' %9.2f `inc_hci'
669     }
670
671 * model 2: adjusted for non-linear covariate change
672 foreach med in bgrade sleep sf_bp ahei illf pa4 alc3 smoke {
673 *   quietly xtreg c_fwd_bmi i.pmix sp age_b age bmi c_ghq10 b0.cd_ghq#c.c_ghq10 c_`med'
    b0.cd_`med'#c.c_`med' if sel_fwdchg<. & c_`med'<.
674     quietly xtreg c_fwd_bmi i.pmix sp age_b age bmi c_ghq10 b0.cd_ghq#c.c_ghq10 `med' if
    sel_fwdchg<. & `med'<.
675     tempvar dec_b inc_b dec_lci inc_lci dec_hci inc_hci
676     quietly lincom c_ghq10 + 0.cd_ghq#c.c_ghq10
677     gen `dec_b'=r(estimate)
678     gen `dec_lci'=r(estimate)-(1.96*r(se))
679     gen `dec_hci'=r(estimate)+(1.96*r(se))
680     quietly lincom c_ghq10 + 1.cd_ghq#c.c_ghq10
681     gen `inc_b'=r(estimate)
682     gen `inc_lci'=r(estimate)-(1.96*r(se))
683     gen `inc_hci'=r(estimate)+(1.96*r(se))
684     di as result %9.2f `dec_b' " " %9.2f `dec_lci' %9.2f `dec_hci' " " ///
685     %9.2f `inc_b' " " %9.2f `inc_lci' %9.2f `inc_hci'
686     }
```

```
//  Table 11-1.
//  P-values for interaction effects of moderator variables in different statistical models.
//  per variable

matrix moda=J(8, 4, .)
local icol 0
foreach moda in sp age bgrade aika {
local ++icol
* cross-sectional
xtlogit ob sp i.pmix age b0.d_ghq##c.`moda' if sel_crs<.
lincom 1.d_ghq#c.`moda'
matrix moda[1, `icol']=(1-(normal((abs(r(estimate))/r(se)))))*2
* lagged associations
xtlogit d_ghq sp i.pmix age c.lag_ob##c.`moda'  if sel_lag<.
lincom c.lag_ob#c.`moda'
matrix moda[2, `icol']=(1-(normal((abs(r(estimate))/r(se)))))*2
xtlogit ob sp i.pmix age c.lag_dghq##c.`moda' if sel_lag<.
lincom c.lag_dghq#c.`moda'
matrix moda[3, `icol']=(1-(normal((abs(r(estimate))/r(se)))))*2
* concurrent change
xtreg c_ghq i.pmix sp age c.c_bmi##c.`moda' if sel_chg<.
lincom c.c_bmi#c.`moda'
matrix moda[4, `icol']=(1-(normal((abs(r(estimate))/r(se)))))*2
* BMI change -> GHQ change
xtreg c_fwd_ghq i.pmix sp age ghq c.c_bmi##c.`moda' ///
b0.cd_bmi#c.c_bmi b0.cd_bmi#c.`moda' b0.cd_bmi#c.c_bmi#c.`moda' if sel_fwdchg<.
    lincom c.c_bmi#c.`moda' + 0.cd_bmi#c.c_bmi + 0.cd_bmi#c.c_bmi#c.`moda'
    matrix moda[5, `icol']=(1-(normal((abs(r(estimate))/r(se)))))*2
    lincom c.c_bmi#c.`moda' + 1.cd_bmi#c.c_bmi + 1.cd_bmi#c.c_bmi#c.`moda'
    matrix moda[6, `icol']=(1-(normal((abs(r(estimate))/r(se)))))*2

* GHQ change -> BMI change
xtreg c_fwd_bmi i.pmix sp bmi age ///
c.c_ghq##c.`moda' b0.cd_ghq#c.c_ghq b0.cd_ghq#c.`moda' b0.cd_ghq#c.c_ghq#c.`moda' if
sel_fwdchg<.
    lincom c.c_ghq#c.`moda' + 0.cd_ghq#c.c_ghq + 0.cd_ghq#c.c_ghq#c.`moda'
    matrix moda[7, `icol']=(1-(normal((abs(r(estimate))/r(se)))))*2
    lincom c.c_ghq#c.`moda' + 1.cd_ghq#c.c_ghq + 1.cd_ghq#c.c_ghq#c.`moda'
    matrix moda[8, `icol']=(1-(normal((abs(r(estimate))/r(se)))))*2
    }
matrix colnames moda=sp age bgrade aika
matrix rownames moda=1_cross 2_ob_ghq 3_ghq_ob 4_cbmi_cghq ///
5_dbmi_fghq 6_ibmi_fghq 7_dghq_fbmi 8_ighq_fbmi
matrix list moda, format(%9.2f)
```

```
//  Figure 1-2. Smoothed distributions of BMI and GHQ score by study phases.
* left-hand panel
local var bmi
kdensity `var' if aika==1, addplot(kdensity `var' if aika==3 || kdensity `var' if aika==5 || ///
kdensity `var' if aika==7 || kdensity `var' if aika==9) ///
legend(label(1 "Phase 1") label(2 "Phase 3") label(3 "Phase 5") label(4 "Phase 7") label(5
"Phase 9") ///
pos(2) ring(0)) ///
title("") ///
xtitle("Body mass index (kg/m2)") ///
ytitle("Percentage of participants") ylabel(,angle(0)) ///
note("") graphregion(color(white))

* right-hand panel
local var ghq
kdensity `var' if aika==1, bw(2.5) addplot(kdensity `var' if aika==3, bw(2.5) || kdensity `var'
if aika==5, bw(2.5) || ///
kdensity `var' if aika==7, bw(2.5) || kdensity `var' if aika==9, bw(2.5)) ///
legend(label(1 "Phase 1") label(2 "Phase 3") label(3 "Phase 5") label(4 "Phase 7") label(5
"Phase 9") ///
pos(2) ring(0)) ///
title("") ///
xtitle("GHQ score") ///
ytitle("Percentage of participants") ylabel(,angle(0)) ///
note("") graphregion(color(white))
```

```
//  Figure 1-3. Smoothed distributions of 5-year changes in BMI and GHQ score by study phases
* left-hand panel
local var c_bmi
kdensity `var' if aika==1, addplot(kdensity `var' if aika==3 || kdensity `var' if aika==5 || ///
kdensity `var' if aika==7) ///
legend(label(1 "Phase 1") label(2 "Phase 3") label(3 "Phase 5") label(4 "Phase 7") ///
pos(2) ring(0)) ///
title("") ///
xtitle("Change in body mass index (kg/m2)") ///
ytitle("Percentage of participants") ylabel(,angle(0)) ///
note("") graphregion(color(white))

* right-hand panel
local var c_ghq
kdensity `var' if aika==1, bw(1.5) addplot(kdensity `var' if aika==3, bw(1.5) || kdensity `var'
if aika==5, bw(1.5) || ///
kdensity `var' if aika==7, bw(1.5)) ///
legend(label(1 "Phase 1") label(2 "Phase 3") label(3 "Phase 5") label(4 "Phase 7") ///
pos(2) ring(0)) ///
title("") ///
xtitle("Change in GHQ score") ///
ytitle("Percentage of participants") ylabel(,angle(0)) ///
note("") graphregion(color(white))
```

```
781 //  Figure 3-1. Mean body mass index, obesity prevalence, and 5-year change in BMI plotted
    against age, adjusted for sex, birth year, and attrition.
782 * BMI trajectory
783 reg bmi sp age_b i.pmix i.age
784 margins, at(sp=(0.30) age_b=(44.2) 0.pmix=(0.77) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.06)
    4.pmix=(0.05)) by(age)
785 * Obesity trajectory
786 logistic ob sp age_b i.pmix i.age
787 margins, at(sp=(0.30) age_b=(44.2) 0.pmix=(0.77) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.06)
    4.pmix=(0.05)) by(age)
788 * BMI change score
789 reg c_bmi sp age_b i.pmix i.age
790 margins, at(sp=(0.29) age_b=(44.1) 0.pmix=(0.83) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.05)
    4.pmix=(0.00)) by(age)
```

```
792 //  Figure 3-2. Mean GHQ score, GHQ caseness prevalence, and 5-year change in GHQ plotted
    against age, adjusted for sex, birth year, and attrition.
793 * GHQ trajectory
794 reg ghq sp age_b i.pmix i.age
795 margins, at(sp=(0.30) age_b=(44.2) 0.pmix=(0.77) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.06)
    4.pmix=(0.05)) by(age)
796 * GHQ caseness trajectory
797 logistic d_ghq sp age_b i.pmix i.age
798 margins, at(sp=(0.30) age_b=(44.2) 0.pmix=(0.77) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.06)
    4.pmix=(0.05)) by(age)
799 * GHQ change score
800 reg c_ghq sp age_b i.pmix i.age
801 margins, at(sp=(0.29) age_b=(44.1) 0.pmix=(0.83) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.05)
    4.pmix=(0.00)) by(age)
```

```
803 //  Figure 3-3. Illustrating the effect of adjusting for birth cohort effects when assessing age
    trajectories in obesity and GHQ caseness prevalence.
804     * no adjustments for obesity
805     logistic ob sp i.pmix i.age
806     margins, at(sp=(0.30) 0.pmix=(0.77) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.06) 4.pmix=(0.05))
    by(age) nose
807     logistic ob sp i.age
808     margins, at(sp=(0.30)) by(age) nose
809
810     * no adjustments for GHQ
811     logistic d_ghq sp i.pmix i.age
812     margins, at(sp=(0.30) 0.pmix=(0.77) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.06) 4.pmix=(0.05))
    by(age) nose
813     logistic d_ghq sp i.age
814     margins, at(sp=(0.30)) by(age) nose
```

```
836 //  Figure 4-1. Risk of obesity as a function of number of times the person has been obese up to
    the previous study phase.
837 xtlogit fwd_dghq i.pmix i.aika age sp b0.ghq_c, or
838 margins, atmeans by(aika ghq_c) predict(pu0)
839
840 //  Figure 4-2. Risk of GHQ caseness as a function of number of times the person has been a GHQ
    case up to the previous study phase.
841 xtlogit fwd_ob i.pmix i.aika age sp b0.ob_c, or
842 margins, atmeans by(aika ob_c) predict(pu0)
843
844 table ob_c aika, c(mean fwd_ob)
845 table ghq_c aika, c(mean fwd_dghq)
```

```
//  Figure 8-1. Non-linear change versus change analysis of BMI and GHQ.
//  Lagged change scores as non-linear exposure
* left-hand panel
xtreg c_fwd_ghq i.pmix sp age_b age ghq c.dc_bmi#c.c_bmi if sel_fwdchg<.
    margins, atmeans at(dc_bmi=(1) c_bmi=(-5 -4 -3 -2 -1 0)) ///
    at(dc_bmi=(0) c_bmi=(1 2 3 4 5))
* right-hand panel
xtreg c_fwd_bmi i.pmix sp age_b age bmi c.cd_ghq#c.c_ghq10 if sel_fwdchg<.
    margins, atmeans at(cd_ghq=(0) c_ghq10=(-3 -2 -1 0)) ///
    at(cd_ghq=(1) c_ghq=(1 2 3))
```

```
//  Figure 9-1. Associations between cumulative score of obesity predicting future GHQ score,
and cumulative GHQ score predicting future BMI.
* left-hand panel
xtreg fwd_ghq i.pmix i.aika age sp b0.ob_c
margins, atmeans by(ob_c)
xtreg fwd_ghq i.pmix i.aika age sp b0.ob_c, fe
margins, atmeans by(ob_c)
xtreg fwd_ghq i.pmix i.aika age sp ob_c
xtreg fwd_ghq i.pmix i.aika age sp ob_c, fe

* right-hand panel
xtreg fwd_bmi i.pmix i.aika age sp b0.ghq_c
margins, atmeans by(ghq_c)
xtreg fwd_bmi i.pmix i.aika age sp b0.ghq_c, fe
margins, atmeans by(ghq_c)
xtreg fwd_bmi i.pmix i.aika age sp ghq_c
xtreg fwd_bmi i.pmix i.aika age sp ghq_c, fe

tab ob_c if fwd_ghq<.
tab ghq_c if fwd_bmi<.
```

```
//  Figure 11-1. Interaction effects between GHQ caseness and age in predicting obesity in
cross-sectional and longitudinal setting.
* left-hand panel
xtlogit ob sp i.pmix b0.d_ghq##c.age##c.age if sel_crs<., or pa
margins, by(d_ghq age) at(sp=(0.30) 0.pmix=(0.77) 1.pmix=(0.08) 2.pmix=(0.04) 3.pmix=(0.06)
4.pmix=(0.05)) noatlegend
* right-hand panel
xtlogit ob sp i.pmix b0.lag_dghq##c.age if sel_lag<., pa
margins, by(lag_dghq age) at(sp=(0.29) 0.pmix=(0.84) 1.pmix=(0.07) 2.pmix=(0.04) 3.pmix=(0.05))
noatlegend
```